HERMES DECLARATION
EXHIBIT 15 – PART 6 OF 8

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office

February 04, 2005

THIS IS TO CERTIFY THAT ANNEXED IS A TRUE COPY FROM THE RECORDS OF THIS OFFICE OF THE FILE WRAPPER AND CONTENTS OF:

APPLICATION NUMBER: *07/838,511*
FILING DATE: *February 19, 1992*
PATENT NUMBER: *5,314,446*
ISSUE DATE: *May 24, 1994*

By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS

N. WOODSON
Certifying Officer

PART 2 OF 2 PART(S)

Form [illegible]

List of Prior Art Cited by Applicant

Serial No. 07/838,594

Applicant Alastair Hunter et al.

Group 1504

2-19-92

U.S. PATENT DOCUMENTS

Exam'r Init.		Document No.	Date	Name	Class	Sub Class	File Date
CWR	AA	3,942,532	3/9/76	Hunter et al.	128	335.5	8/15/74
CWR	AB	4,624,256	11/25/86	Messier et al.	128	335.5	8/11/85
CWR	AC	3,527,650	9/8/70	Block, A.	117	7	12/21/67
CWR	AD	4,470,941	9/11/84	Kurtz, L.	264	136	6/2/82
CWR	AE	3,187,752	6/8/65	Glick, A.	128	335.5	4/27/62
CWR	AF	4,043,344	8/23/77	Landi et al.	128	335.5	9/20/76
CWR	AG	4,047,533	8/13/77	Perciaccante et al.	128	335.5	9/20/76
CWR	AH	4,946,467	8/7/90	Ohi et al.	606	228	3/8/89
	AI						
	AJ						
	AK						

FOREIGN PATENT DOCUMENTS

Exam'r Init.		Document No.	Date	Country	Class	Sub Class	Translate Yes	Translate No
CWR	AL	GB 2 218 312A	11/15/89	United Kingdom	A01K	91/00	✓	—
CWR	AM	DE 2949920	3/19/81	Germany	A61F	1/00	✓	—
CWR	AN	WO 86/00020	1/3/86	PCT	A61L	17/00	✓	—
	AO							
	AP							

OTHER REFERENCES (include author, title, date, pertinent pages, etc.)

	AR		
	AS		
	AT		

Examiner	Date Considered
CHRIS RAIMUND	JUNE 25, 1992

*Examiner: See note on original PTO form concerning initialing and MPEP 609 compliance. Include copy of this form with next communication to applicant.

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

Address : COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
07/828,511	02/19/92	HUNTER A	ETH-782

ROBERT L. MINIER
ONE JOHNSON & JOHNSON PLAZA
NEW BRUNSWICK, NJ 08933-7003

EXAMINER	
RAIMUND J.C	3
ART UNIT	PAPER NUMBER
1504	

DATE MAILED: 07/08/92

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☑ This application has been examined ☐ Responsive to communication filed on _____ ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), ___ days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☑ Notice re Patent Drawing, PTO-948.
3. ☑ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, Form PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☑ Claims 1 - 24 are pending in the application.
   Of the above, claims 1 - 20 are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☑ Claims 21 - 24 are rejected.
5. ☐ Claims _____ are objected to.
6. ☑ Claims 1 - 24 are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed on _____ has been ☐ approved. ☐ disapproved (see explanation).
12. ☐ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____ ; filed on _____
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

PTOL-326 (Rev. 9-89)

Restriction to one of the following inventions is required under 35 U.S.C. § 121:

I. Claims 1-20, drawn to a heterogeneous braid, classified in Class 57, subclass 243.

II. Claims 21-24, drawn to a surgical suture, classified in Class 600, subclass 231.

The inventions are distinct, each from the other because of the following reasons:

Inventions I and II are related as mutually exclusive species in intermediate-final product relationship. Distinctness is proven for claims in this relationship if the intermediate product is useful to make other than the final product (M.P.E.P. § 806.04(b), 3rd paragraph), and the species are patentably distinct (M.P.E.P. § 806.04(h)).

In the instant case, the intermediate product is deemed to be useful as a fishing line and the inventions are deemed patentably distinct since there is nothing on this record to show them to be obvious variants. Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record

showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions anticipated by the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. § 103 of the other invention.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter, restriction for examination purposes as indicated is proper.

During a telephone conversation with Matthew S. Goodwin on June 23, 1992 a provisional election was made without traverse to prosecute the invention of Group II, claims 21-24. Affirmation of this election must be made by applicant in responding to this Office action. Claims 1-20 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b), as being drawn to a non-elected invention.

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claims 21-24 are rejected under 35 U.S.C. § 103 as being unpatentable over Burgess (U.K. Patent Application No. 2,218,312A).

Burgess discloses a fishing line of braided construction comprising filaments of polyethylene and filaments of polyester or nylon. Such a braid is disclosed to have the low stretchability of polyethylene and the low coefficient of friction of polyester. (See page 1). It is therefore known to braid filaments of two dissimilar polymers together to form a structure which embodies the desirable properties of each fiber.

Braided sutures are well known in the art. Many of the requirements of sutures are comparable to those of fishing line- strength, low stretchability, flexibility, low coefficient of friction etc. Indeed, many of the same materials are used for both of these applications. It would therefore have been

obvious, in view of Burgess, to use a heterogeneous braid for a suture. Claims 21 and 23 are therefore unpatentable over Burgess.

Synthetic, fiber forming polymers are widely employed as filaments in braided sutures. In German Patent Application DE 2949920A1, for example, surgical sutures made from braided polytetrafluoroethylene (PTFE) fibers or polyester fibers are disclosed. As polyester fibers are noted for their strength and PTFE fibers for their low coefficient of friction, it would have been obvious to use a braid comprising both types of filaments as a suture.

It is also known in the art to a braid around longitudinally extending core filaments. Ohi et al, for example, disclosure a core comprising a plurality of synthetic fiber filaments (column 1, lines 57-60). Polyester filament are specifically disclosed (column 2, lines 4-9). It would therefore have been obvious to dispose a heterogeneous braid comprising polyester and polytetrafluoroethylene fibers around a core of polyester fibers to form a suture. Claims 22 and 24 are therefore unpatentable over Burgess.

Any inquiry concerning this communication should be directed to Chris Raimund at telephone number (703) 308-3452.

Chris Raimund:jp
July 06, 1992

GEORGE F. LESMES
SUPERVISORY PATENT EXAMINER
GROUP 150

PTO FORM 948
(Rev 5-91)

U.S. DEPARTMENT OF COMMERCE
Patent and Trademark Office

ATTACHMENT TO PAPER NUMBER 3

APPLICATION NUMBER 838511

GROUP 1504

NOTICE OF DRAFTSMAN'S PATENT DRAWING REVIEW

The PTO Draftsmen review all originally filed drawings regardless of whether they were designated as informal or formal.

The drawings filed 2/19/92

A. ☒ are approved.

B. ☐ are objected to under 37 CFR 1.84 for reason(s) checked below. The examiner will require submission of new, corrected drawings at the appropriate time. Corrected drawings must be submitted according to the instructions listed on the back of this Notice.

1. Paper and ink. 37 CFR 1.84(a)
   - ☐ Poor Quality Paper. Must Be White. Transparent Paper Not Allowed. Sheet(s) _____

2. Size of Sheet and Margins. 37 CFR 1.84(b)

   Acceptable Paper Sizes and Margins

Margin	Paper Size: 8 1/2 by 14 inches	8 1/2 by 13 inches	DIN size A4 21 by 29.7 cm.
Top	2 inches	1 inch	2.5 cm.
Left	1/4 inch	1/4 inch	2.5 cm.
Right	1/4 inch	1/4 inch	1.5 cm.
Bottom	1/4 inch	1/4 inch	1.0 cm.

   - ☐ Proper Size Paper Required. All Sheets Must be Same Size. Sheet(s) _____
   - ☐ Proper Margins Required. Sheet(s) _____
     - ☐ Top ☐ Right
     - ☐ Left ☐ Bottom

3. Character of Lines. 37 CFR 1.84(c)
   - ☐ Lines Pale, Rough and Blurred, or Jagged. Fig(s) _____
   - ☐ Solid Black Shading Not Allowed. Fig(s) _____

4. ☐ Photographs Not Approved. _____

5. Hatching and Shading. 37 CFR 1.84(d)
   - ☐ Shade Lines are Required. Fig(s) _____
   - ☐ Criss-Cross Hatching Not Allowed. Fig(s) _____
   - ☐ Double Line Hatching Not Allowed. Fig(s) _____
   - ☐ Parts in Section Must be Hatched Properly. Fig(s) _____

6. Reference Characters. 37 CFR 1.84(f)
   - ☐ Reference Characters Poor or Rough and Blurred. Fig(s) _____
   - ☐ Minimum 1/8 inch (3.2 mm.) in height is required. Fig(s) _____
   - ☐ Figure Legends Poor or Placed Incorrectly. Fig(s) _____

7. Views. 37 CFR 1.84(i) & (j)
   - ☐ Figures Must be Numbered Separately. _____
   - ☐ Figures Must Not be Connected Fig(s) _____

8. Identification of Drawings. 37 CFR 1.84(l)
   - ☐ Extraneous Matter or Copy Machine Marks Not Allowed. Fig(s) _____

9. ☐ Changes Not Completed from Prior PTO-948 dated _____

☐ Comments:

DePuy Mitek, Inc. v. Arthrex, Inc.
C.A. No.04-12457 PBS
DMI000191

Telephone inquires concerning this review should be directed to the Chief Draftsman at telephone number (703) 557-6404.

_____ 3/6/92
Reviewing Draftsman — Date

PTO Copy

INFORMATION ON HOW TO EFFECT DRAWING CHANGES

1. **Correction of Informalities—37 CFR 1.85**
File new drawings with the changes incorporated therein. The art unit number, serial number and number of drawing sheets should be written on the drawings in accordance with 37 CFR 1.84(f). Applicant may delay filing of the new drawings until receipt of the "Notice of Allowability" (PTOL-37). If delayed, the new drawings **MUST** be filed within the **THREE MONTH** shortened statutory period set for response in the "Notice of Allowability" (PTOL-37). Extensions of time may be obtained under the provisions of 37 CFR 1.136 The drawing should be filed as a separate paper with a transmittal letter addressed to the Official Draftsman.

   Timing of Corrections
   Applicant is required to submit **acceptable** corrected drawings within the three month shortened statutory period set in the "Notice of Allowability" (PTOL-37). Within that three month period, two weeks should be allowed for review by the Office of the correction. If a correction is determined to be unacceptable by the Office, applicant must arrange to have acceptable correction re-submitted within the original three month period to avoid the necessity of obtaining an extension of time and paying the extension fee. Therefore, applicant should file corrected drawings as soon as possible.

   Failure to take corrective action within set (or extended) period will result in **ABANDONMENT** of the Application.

2. **Corrections other than Informalities Noted by the Draftsman on the PTO-948**
All changes to the drawings, other than informalities noted by the Draftsman, **MUST** be made in the same manner as above except that, normally, a red ink sketch of the changes to be incorporated into the new drawings **MUST** be approved by the examiner before the application will be allowed. No changes will be permitted to be made, other than correction of informalities, unless the examiner has approved the proposed changes.

ETH 782
Batch No. 567

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Alastair W. Hunter et al.

Serial No.: 838,511 Art Unit: 1504

Filed : February 19, 1992 Examiner: C. Raimund

For : **STERILIZED HETEROGENOUS BRAIDS**

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231 on

February 14, 1994
(Date of Deposit)

Hal Brent Woodrow
Name of applicant, assignee, or Registered Representative

Hal Brent Woodrow
(Signature)

February 14, 1994
(Date of Signature)

9200 ordered 5/18/94

Hon. Commissioner of Patents
and Trademarks
Washington, D.C. 20231

AMENDMENT UNDER 37 CFR §312

Dear Sir:

This is responsive to the Examiner's Amendment attached to the Notice of Allowance dated November 15, 1993, at which time a shortened statutory period for response of three months was set.

In the Claims

Please amend the claims as follows:

In Claim 10 after "claim" and before "wherein" please delete "8" and insert therefor -- 21 -- .

OK to enter - 9/4/

Hal Brent Woodrow
Hal Brent Woodrow
Reg. No. 32,501
Attorney for Applicant(s)

ETH-78

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Alastair Hunter et al.

Serial No.: 838,511 Art Unit: 1504

Filed : February 19, 1992 Examiner: C. Raimund

For : STERILIZED HETEROGENEOUS BRAIDS

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231 on

August 6, 1992
(Date of Deposit)

Matthew S. Goodwin
Name of applicant, assignee, or Registered Representative

(Signature)

August 6, 1992
(Date of Signature)

Hon. Commissioner of Patents
and Trademarks
Washington, D.C. 20231

AMENDMENT

Dear Sir:

Responsive to the Office Action of July 8, 1992, please reconsider the above-identified application in view of the following remarks.

REMARKS

1. Restriction to the invention of either Group I, claims 1-20, or Group II, claims 21-24, was required. Applicants reaffirm without traverse to prosecute the invention of Group II, claims 21-24. This election is made without prejudice to Applicants' right to file a divisional application directed to the non-elected invention of Group I, claims 1-20.

2. Claims 21-24 were rejected under 35 USC §103 as being unpatentable over Burgess. The Examiner has asserted that it would have been obvious in view of Burgess to use a heterogeneous braid for a suture. Applicants respectfully traverse this rejection.

The Examiner mistakenly believes that the requirements for a braided suture are comparable to those of a fishing line. However, nothing could be further from the truth.

One of the most important requirements for a braided suture is that it have outstanding knot strength when a knot is secured on the suture braid. Indeed, this requirement may be the most important requirement for a braided suture. This is so because the suture knot is what keeps a stitched wound intact. If the knot fails, then the wound can reopen and consequently the braided suture has failed as well.

Applicants recognized the importance of knot strength when attempting to overcome the shortcomings of the braided sutures disclosed in the art. In preferred embodiments of the invention, Applicants' claimed suture exhibits improved handling properties without sacrificing physical strength or knot security (see the specification at page 5, lines 4-7). In addition, numerous braided sutures were tested to determine their knot strength and knot security (see the examples at the end of the specification). The determination of knot security is described in the specification at page 12, lines 26-33.

In contrast, knot strength is not even mentioned in Burgess. Although it may be argued that it may be necessary to secure a knot on a fishing line to hold the hook to the line, the security and strength of the knot are not nearly as critical for this application. In fact, the fishing line of Burgess would have poor knot strength properties because of its braided construction, as set forth in more detail below.

Some of the braid filaments of the Burgess fishing line are composed of high tensile polythene thread. This thread gives the line minimal stretchability (see Burgess at page 1, lines 12-13). Although this thread has great strength properties, it suffers from

low elongation and, in turn, poor knot strength properties. This is a good idea for a fishing line because high strength and low elongation, or low stretchability, are important criteria. Low elongation is an important requirement for a fishing line because it makes it possible for the fisherman to apply force on the hook when, for example, the fish is caught. If the line were stretchable, then the force exerted by the fisherman would be taken up by the stretching action of the line. This would clearly be an undesirable property for a fishing line to exhibit. Therefore, the property requirements for fishing line yield a braid with poor knot strength and security, and the requirements for sutures yield a braid which has by necessity excellent knot strength and security.

In addition to the contrasting requirements for braided sutures and fishing line resulting from the critical need to tie strong and secure knots on braided sutures, other requirements concerning the knot make the braid for a fishing line unsuitable for use as sutures. For example, a surgeon must be able to make a conventional square knot at a very fast pace for patient safety. Clearly, a knot on a fishing line for a hook can be made at a much slower pace, and with a much more complex knot. Also, it is necessary during suturing to form a pre-knot on the braided suture, and the pre-knot must be subsequently slid down the suture until it is adjacent the body tissue desired to be stitched. Once the knot is placed at the desired location, additional throws on the knot can be added for knot security. This requires a braided suture which is stretchable and resilient so that this operation can be performed. Obviously, there is no such similar requirement for a fishing line.

In view of the dissimilarities in property requirements between sutures and fishing line, there would simply be no incentive for a medical designer who wishes to improve the properties of braided sutures to study the art related to braided fishing lines. Even if he did use the teachings of the fishing line art to modify a

suture, then he would inevitably design an unacceptable suture. Accordingly, Applicants respectfully submit that the rejection is in error and therefore it should be withdrawn.

It is noted that the Examiner has discussed German Patent Application DE 2949920 A 1 and Ohi et al. as evidence of the state of the art concerning the types of filaments used in braided sutures, and core/sheath braid construction. Applicants do not wish to rely on these specific limitations set forth in claims 22 and 24 for patentability, but instead rely on the inventive features set forth in the broader independent claim, claim 21.

Accordingly, for the reasons set forth above, Applicants respectfully request the Examiner to withdraw the rejection of claims 21-24 under 35 USC 103 as being unpatentable over Burgess.

3. Since all formal requirements appear to have been met, except for the submission of formal drawings, and claims 21-24 are patentable over the art of record, Applicants respectfully solicit a Notice of Allowability.

Respectfully submitted,

Matthew S. Goodwin
Attorney for Applicant
Reg. No. 32,839

Johnson & Johnson
One Johnson & Johnson Plaza
New Brunswick, New Jersey 08933-7003
(908) 524-2791
August 6, 1992

Case Docket No.: ETH-782

In application of Alastair Hunter et al.

Serial No. 838,511

Filed February 19, 1992

For STERILIZED HETEROGENEOUS BRAIDS

THE COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

Sir:

Transmitted herewith is an amendment in the above-identified application.

[ ] No additional fee is enclosed because this application was filed prior to October 25, 1965 (effective date of Public Law 89-83).

[X] No additional fee is required.

[X] One stamped, self-addressed postcard for the PTO Mail Room date stamp.

[ ] Petition For Extension of Time and charge to Deposit Account of Appropriate Fee.

The fee has been calculated as shown below.

CLAIMS AS AMENDED

(1)	(2)	(3)	(4)	(5)	(6)	(7)
	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NO. PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE	ADDITIONAL FEE
TOTAL CLAIMS	* XX	minus	** XX	= 0	x $20	= $ XXX.XX
INDEP. CLAIMS	* XX	minus	*** XX	= XX	x $72	= $ XXX.XX
			TOTAL ADDITIONAL FEE FOR THIS AMENDMENT			$ XXX.XX

* If the entry in Col.2 is less than the entry in Col.4, write "0" in Col.5
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, write "20" in this space.
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, write "3" in this space.

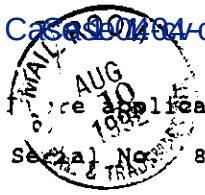
[ ] Charge $ ###.## to Deposit Account No. 10-750/DOCKET NO/ATTY. Three copies of this sheet are enclosed.

[X] Please charge any additional fees in connection with the filing of this communication, or credit overpayment, to Deposit Account No. 10-750/ETH-782/MSG. Three copies of this sheet are enclosed.

[ ] A check in the amount of $ _____ is attached.

Matthew S. Goodwin
Attorney of Record
Reg. No. 32,839

Matthew S. Goodwin
Johnson & Johnson
One Johnson & Johnson Plaza
New Brunswick, New Jersey 08933-7003
(908) 524-2791
August 6, 1992



Case Docket No.: ETH-782

In re application of Alastair Hunter et al.

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TOTAL CLAIMS	* XX	minus	** XX	= 0	x $20	= $ XXX.XX
INDEP. CLAIMS	* XX	minus	*** XX	= XX	x $72	= $ XXX.XX
			TOTAL ADDITIONAL FEE FOR THIS AMENDMENT			$ XXX.XX

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*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, write "3" in this space.

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[ ] A check in the amount of $ _____ is attached.

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Case Docket No.: ETH-782

In the application of Alastair Hunter et al.

Serial No. 838,511

Filed February 19, 1992

For STERILIZED HETEROGENEOUS BRAIDS

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AUG 17 1992
GROUP 150

THE COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

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The fee has been calculated as shown below.

CLAIMS AS AMENDED

(1)	(2)	(3)	(4)	(5)	(6)	(7)
	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NO. PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE	ADDITIONAL FEE
TOTAL CLAIMS	* XX	minus	** XX	= 0	x $20	= $ XXX.XX
INDEP. CLAIMS	* XX	minus	*** XX	= XX	x $72	= $ XXX.XX
			TOTAL ADDITIONAL FEE FOR THIS AMENDMENT			$ XXX.XX

* If the entry in Col.2 is less than the entry in Col.4, write "0" in Col.5
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, write "20" in this space.
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, write "3" in this space.

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August 6, 1992

Address : COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ART UNIT	ATTORNEY DOCKET NO.
07/785,111	11/13/92	HUNTER A		

RAIMUND, C
EXAMINER

5
PAPER NUMBER

1811
ART UNIT

ROBERT L. MINIER
ONE JOHNSON & JOHNSON PLAZA
NEW BRUNSWICK, NJ 08933-7003

11/02/92
DATE MAILED:

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☐ This application has been examined ☑ Responsive to communication filed on August 6, 1992 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), ___ days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☑ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice re Patent Drawing, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, Form PTO-152
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☑ Claims 1 - 24 are pending in the application.
   Of the above, claims 1 - 20 are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☑ Claims 21 - 24 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____, has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

PTOL-326 (Rev.9-89)

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 21 and 23 are rejected under 35 U.S.C. § 102(b) as being clearly anticipated by Doddi et al.

Doddi et al disclose a surgical suture comprising filaments of two different polymers in a braided configuration (column 9, lines 47-56). The suture is specifically disclosed attached to a needle (column 11, lines 53-54). Claims 21 and 23 are therefore unpatentable over Doddi et al.

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claims 22 and 24 are rejected under 35 U.S.C. § 103 as being unpatentable over Kaplan et al taken with Doddi et al.

Kaplan et al discloses a ligament prosthesis comprising a core component and a braided sheath component (see Figure 3). The core component is "made up of one or more biocompatible, essentially non-bioasborbable..." filaments (column 9, lines 1-3). The sheath yarn component may be fabricated "from individual filaments having more than two different chemical compositions, one or more of which optionally being nonbioabsorbable" (column 9, lines 25-28).

Doddi et al disclose suitable biocompatible, non-absorbable fibers to include PET and PTFE (column 9, lines 51-53). It would have been obvious to form the device of Kaplan with a sheath component of PTFE and PET and a core component of PET. PTFE is known to impart improved knot run down properties to sutures (see Block U.S. Patent No. 3,527,650). PET is noted for its low cost

and high strength. Claims 22 and 24 are therefore unpatentable over Kaplan et al taken with Doddi et al.

Applicant's arguments with respect to claims 21-24 have been considered but are deemed to be moot in view of the new grounds of rejection.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Any inquiry concerning this communication should be directed to Chris Raimund at telephone number (703) 308-3452.

Chris Raimund:jp
October 29, 1992

GEORGE F. LESMES
SUPERVISORY PATENT EXAMINER
GROUP 150

FORM PTO-892 (REV. 2-92) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

NOTICE OF REFERENCES CITED

SERIAL NO.	GROUP ART UNIT	ATTACHMENT TO PAPER NUMBER
838,511	1504	

APPLICANT(S): Hunter et al.

U.S. PATENT DOCUMENTS

*		DOCUMENT NO	DATE	NAME	CLASS	SUB-CLASS	FILING DATE IF APPROPRIATE
	A	4052988	10/1977	Daddi et al.	128	335.5	—
	B	5147400	09/1992	Kaplan et al.	623	13	09/1990
	C	5116360	05/1992	Pinchuk et al.	623	1	12/1990
	D						
	E						
	F						
	G						
	H						
	I						
	J						
	K						

FOREIGN PATENT DOCUMENTS

*		DOCUMENT NO.	DATE	COUNTRY	NAME	CLASS	SUB-CLASS	PERTINENT SHTS DWG	PERTINENT PP. SPEC.
	L								
	M								
	N								
	O								
	P								
	Q								

OTHER REFERENCES (Including Author, Title, Date, Pertinent Pages, Etc.)

R

S

T

U

EXAMINER: CHRIS RAIMUND

DATE: OCT. 26, 1992

* A copy of this reference is not being furnished with this office action. (See Manual of Patent Examining Procedure, section 707.05 (a).)

DePuy Mitek, Inc. v. Arthrex, Inc.
C.A. No.04-12457 PBS
DMI000205

XR 4,052,988

United States Patent [19]

Doddi et al.

[11] 4,052,988

[45] Oct. 11, 1977

[54] SYNTHETIC ABSORBABLE SURGICAL DEVICES OF POLY-DIOXANONE

[75] Inventors: Namassivaya Doddi; Charles C. Versfelt, both of Somerville; David Wasserman, Springfield, all of N.J.

[73] Assignee: Ethicon, Inc., Somerville, N.J.

[21] Appl. No.: 648,236

[22] Filed: Jan. 12, 1976

[51] Int. Cl.² A61L 17/00

[52] U.S. Cl. ..... 128/335.5; 3/1; 128/92 B; 128/92 D; 260/78.3 R

[58] Field of Search 128/335.5, 92; 260/78.3; 3/1

[56] References Cited

U.S. PATENT DOCUMENTS

3,063,967	11/1962	Schultz	260/78.3
3,063,968	11/1962	Schultz	260/78.3
3,190,858	6/1965	Cox et al.	260/78.3
3,297,033	1/1967	Schmitt et al.	128/335.5
3,636,956	1/1972	Schneider et al.	128/335.5
3,645,941	2/1972	Snapp et al.	260/78.3
3,867,190	2/1975	Schmitt et al.	128/335.5 X
3,960,152	6/1976	Augurt et al.	128/335.5

OTHER PUBLICATIONS

Palomaa et al.-Ber. Deut. Chem. Gesellsch., vol. 66B, pp. 1629-1632 (1933).

Primary Examiner—Dalton L. Truluck
Attorney, Agent, or Firm—Wayne R. Eberhardt

[57] ABSTRACT

Synthetic absorbable sutures and other surgical devices are prepared from polymers of p-dioxanone and 1,4-dioxepan-2-one, and alkyl substituted derivatives thereof. Monofilament sutures of oriented fibers are characterized by good tensile and knot strength and a high level of flexibility and softness. The sutures have good in vivo strength retention and are slowly absorbed without significant tissue reaction.

39 Claims, 5 Drawing Figures

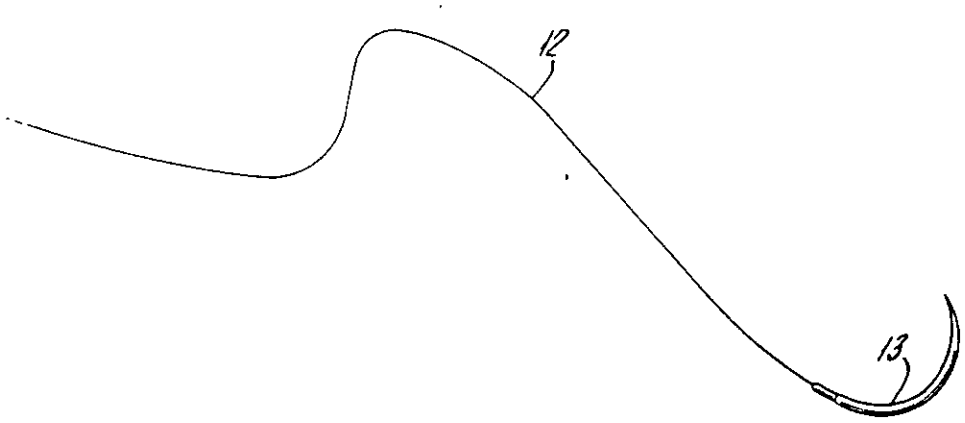


Fig. 1.

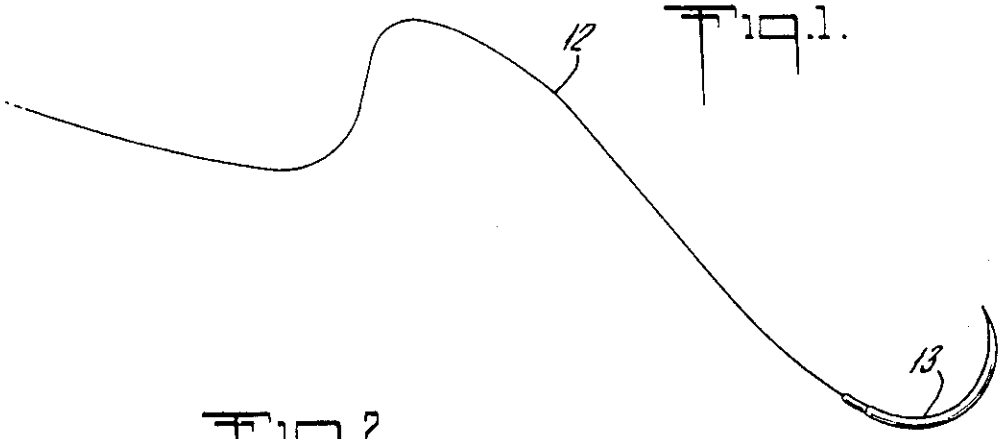


Fig. 2.

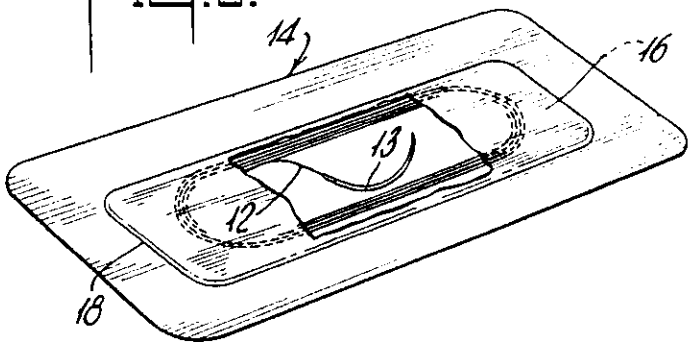


Fig. 3.

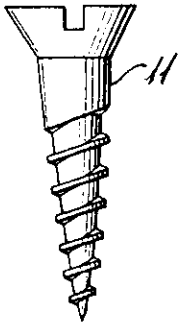


Fig. 4.

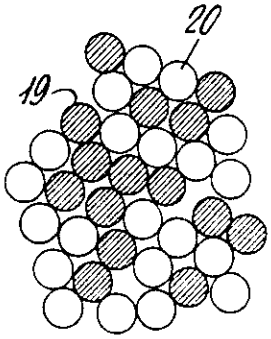
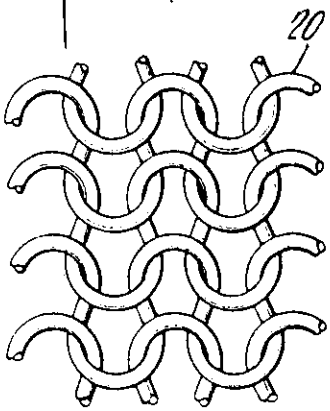


Fig. 5.



SYNTHETIC ABSORBABLE SURGICAL DEVICES OF POLY-DIOXANONE

BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention relates to synthetic absorbable sutures, and more particularly, to synthetic absorbable sutures comprising extruded and oriented filaments of polymers of p-dioxanone or 1,4-dioxepan-2-one.

2. Description of Prior Art

Absorbable suture materials have traditionally been natural collagenous materials obtained from sheep or beef intestine, commonly known as catgut. More recently, it has been proposed to manufacture synthetic absorbable sutures from polyesters of hydroxycarboxylic acids, notably polylactide, polyglycolide, and copolymers of lactide and glycolide. Such synthetic absorbable sutures are described in U.S. Pat. Nos. 3,636,956, 3,297,033 and elsewhere in the literature.

Among the requirements of an ideal absorbable suture are that it should have good handling properties, should approximate and hold tissue for proper healing with minimal tearing and tissue damage, should have adequate straight tensile and knot strength, should be controllably uniform in properties including dimensional stability within the body, should be sterilizable, should be absorbable by living tissue, preferably at a constant rate regardless of the place in the body or the condition of the patient, without causing such unfavorable tissue reactions as walling off, granuloma formation, excessive edema, etc., and finally should be capable of being properly and easily tied into surgical knots.

While multifilament sutures manufactured from polymers of lactide and glycolide fulfill the above requirements to a large degree, monofilament sutures of these materials are considerably less flexible than catgut and these synthetic sutures are accordingly generally limited to a multifilament, braided construction. Sutures of glycolide polymers are also not suitable for sterilization by radiation without suffering severe degradation of physical properties.

The present invention provides synthetic absorbable sutures having a high degree of softness and flexibility which allows the sutures to be used in monofilament form. The sutures can also be sterilized with cobalt 60 radiation without serious loss of suture strength. It is accordingly an object of the present invention to provide synthetic absorbable sutures having unique and desirable properties not available with the sutures of the prior art.

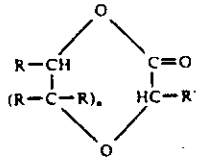
We have discovered that polymers of p-dioxanone and 1,4-dioxepan-2-one prepared from monomers of very high purity can be melt extruded into pliable, monofilament fibers which are slowly absorbed in animal tissue without significant adverse tissue reaction. The fibers have good tensile and knot strength and good in vivo strength retention, and can be sterilized with cobalt 60 without serious loss of these properties.

Polymers of p-dioxanone and fibers extruded therefrom have been known in the art. U.S. Pat. Nos. 3,063,967 and '968 for example, describe the polymerization of p-dioxanone and the preparation of films and fibers therefrom. The low tensile strength of fibers prepared in accordance with the teachings of these references, however, make these fibers generally unsuitable for use as surgical sutures. Moreover, there was no appreciation in these references of the absorbability of such fibers which were reported to be resistent to the effects of saline and distilled water.

Other references dealing with the polymerization of p-dioxanone include, but are not limited to, U.S. Pat. Nos. 3,190,858, 3,391,126 and 3,645,941 which disclose various catalysts for the polymerization of lactones such as p-dioxanone, and U.S. Pat. No. 3,020,289 which describes the polymerization of p-dioxanone in the presence of sulfuric acid. None of these references suggest polymers of p-dioxanone or 1,4-dioxepan-2-one for use in the preparation of synthetic absorbable sutures in accordance with the present invention.

SUMMARY

Synthetic absorbable sutures are prepared from polymers of monomers having the formula:



wherein R' and each R are hydrogen, methyl or ethyl and n is 1 or 2, provided that when n is 2, at least two R groups are hydrogen.

Polymers prepared by the polymerization of very pure monomers are melt extruded into filaments suitable for use as synthetic absorbable sutures. The filaments are characterized by high tensile and knot strength, good strength retention in vivo, and a Young's modulus of less than about 600,000 psi corresponding to a high degree of softness and flexibility.

DESCRIPTION OF DRAWINGS

FIG. 1 is a perspective view of a needle-suture combination;

FIG. 2 is a perspective view of a suture-needle combination within a hermetically sealed container;

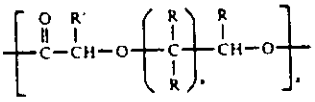
FIG. 3 illustrates a screw machined from the polymer of the present invention;

FIG. 4 is a cross-sectional view of a composite yarn containing filaments of different composition and;

FIG. 5 is a plan view of a surgical fabric knitted from fibers of the present invention.

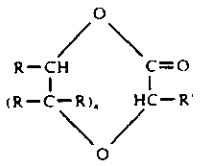
DESCRIPTION OF PREFERRED EMBODIMENTS

Polymers of the present invention are comprised of units having the general formula:



wherein R' and R are individually hydrogen, methyl, or ethyl, n is 1 or 2 provided that when n is 2 at least two R groups are hydrogen, and x is the degree of polymerization resulting in a fiber forming polymer.

The polymer is conveniently prepared from highly purified monomer, i.e., monomer of at least about 98 percent purity, having the formula:



wherein R, R' and *n* are as defined above. When *n* is 1, the monomer is preferably p-dioxanone, methyl-p-dioxanone, or dimethyl-p-dioxanone. When *n* is 2, the monomer is preferably 1,4-dioxepan-2-one.

A particularly preferred monomer is p-dioxanone, and the following description and examples which are presented by way of illustration are directed primarily to the preparation and polymerization of that monomer, it being understood that certain variations may apply to other monomers and polymers encompassed by the above formula as will be readily apparent to those skilled in the art. Para-dioxanone monomer is conveniently prepared by reacting ethylene glycol, metallic sodium, and chloroacetic acid as hereinafter described in detail. The resulting monomer is preferably purified to 99+% purity by multiple distillations and recrystallizations. We have discovered that high monomer purity is necessary to obtain a high molecular weight polymer and ultimately, a fiber of good tensile and dry knot strength.

The purified monomer is polymerized at a temperature of 20° to 130° C, most preferably above 75° C, in the presence of an organometallic catalyst as hereinafter described in detail to obtain a high molecular weight polymer of p-dioxanone characterized by an inherent viscosity of at least about 0.50 measured as a 0.1% solution in tetrachloroethane at 25° C, and a crystallinity of at least about 20% as determined by X-ray diffraction.

The polymer is melt extruded through a spinneret in a conventional manner to form one or more filaments which are subsequently drawn about 4x to 6x in order to achieve molecular orientation and improve tensile properties. The resulting oriented filaments have good tensile and dry knot strength and good in vivo strength retention.

To further improve dimensional stability and tensile strength retention, the oriented filaments may be subjected to an annealing treatment. This optional annealing treatment consists of heating the filaments to a temperature of from about 50° to 105° C, most preferably from about 50° to 80° C while restraining the filaments to prevent any substantial shrinkage. The filaments are held at the annealing temperature for a few seconds to several days or longer depending on the temperature and processing conditions. In general, annealing at 50° to 80° C for up to about 24 hours is satisfactory for p-dioxanone. Optimum annealing time and temperature for maximum improvement in fiber in vivo strength retention and dimensional stability is readily determined for each fiber composition.

Since the function of a suture is to join and hold severed tissue until healing is well along, and to prevent separation as a result of movement or exercise, a suture must meet certain minimum standards of strength. It is particularly important that strength be maintained when knots are tied and during the actual procedure of drawing tight a suitable knot. Oriented filaments of the present invention are characterized by a straight tensile strength of at least about 40,000 psi and a knot strength of at least about 30,000 psi, although significantly higher

strengths are possible as will be apparent from the following examples.

The preparation of high molecular weight oriented filaments of poly-p-dioxanone and other polymers of the present invention is further illustrated by the following examples where all percentages are by weight unless otherwise noted.

EXAMPLE I

A. Preparation of p-dioxanone

Metallic sodium is dissolved in a large excess of ethylene glycol to obtain a glycolate which is further reacted with about 0.5 mols of chloroacetic acid per mole of sodium to yield the sodium salt of the hydroxy acid. Excess ethylene glycol and by-products of the reaction are removed by distillation and by washing with acetone. The sodium salt is converted to the free hydroxy acid by the addition of hydrochloric acid, and the resulting sodium chloride is removed by precipitation with ethanol followed by filtration.

The hydroxy acid filtrate is slowly heated up to about 200° C, preferably in the presence of $MgCO_3$, to remove alcohol and water by distillation. Upon further heating at atmospheric pressure the p-dioxanone is formed and distills over at a head temperature of between about 200°-220° C. The purity of the crude dioxanone product is generally about 60-70 percent as determined by gas chromatography and yields are in the order of 50 to 70 percent.

The crude p-dioxanone is further purified to about 98 percent by redistillation, and finally purified to 99+% by multiple crystallizations and/or distillation.

B. Polymerization of p-dioxanone

Highly purified p-dioxanone is polymerized in the presence of an organometallic catalyst such as diethyl zinc or zirconium acetylacetonate to obtain high molecular weight, fiber forming polymers according to the following typical procedure.

0.1 M (10.2 g) of dry, 99+% pure p-dioxanone monomer is weighed into a dry flask under an inert atmosphere of dry nitrogen and 0.36 ml of 0.138M diethyl zinc in heptane are added. The monomer to catalyst ratio is calculated as 2000 : 1. After completely mixing the catalyst and monomer, the flask is swirled at intervals over a period of about one hour or less at room temperature until initiation and polymerization is evident by the occurrence of gelation. The flask is then connected to a vacuum of about 14 inches of Hg. The sealed flask is maintained at 80° C in a constant temperature bath for about 72 hours to complete the polymerization. The resulting polymer is characterized by an inherent viscosity I.V. of 0.70 measured on a 0.1% solution of polymer in tetrachloroethane at 25° C, a glass transition temperature T_g of −16° C, a melting temperature T_m of 110° C, and a crystallinity of 37 percent.

In the polymerization procedure, the initial one hour hold time for polymerization initiation is required only when using volatile catalysts which would be lost if the polymerization mixture was immediately placed under vacuum. When nonvolatile catalysts such as zirconium acetyl acetonate are used, this hold time may be omitted and the polymerization reaction mixture placed under vacuum immediately following addition and mixing of catalyst. As a further alternative, the entire polymeriza-

tion reaction may be conducted under an inert atmosphere at atmospheric pressure.

C. Polymer Extrusion

The polymer obtained in the preceding step is thoroughly dried and melt extruded through a spinnerette using conventional textile fiber spinning procedures to obtain one or more continuous monofilament fibers suitable for use as synthetic absorbable sutures. The spun filaments are drawn about 5x at a temperature of about 43° C to increase molecular orientation and enhance physical properties, particularly tensile strength. The drawn monofilaments having a diameter of about 11 mils corresponding to a size 2-0 suture are characterized by an inherent viscosity of 0.64, a crystallinity of 30 percent, a straight tensile strength of 36,600 psi, an elongation of 99.4 percent, and a knot strength of 31,900 psi.

EXAMPLE II

The method of Example I was repeated using 0.13 ml of zirconium acetyl acetonate catalyst (7500 : 1 monomer to catalyst ratio) in the polymerization reaction. Properties of polymer and fiber were as follows:

Polymer

I.V.: 0.71
Tg: −16° C
Tm: 111° C
Crystallinity: 49%

Fiber

I.V.: 0.57
Tensile Strength: 38,600 psi
Elongation: 88.5 percent
Knot Strength: 32,300 psi

EXAMPLE III

Polydioxanone polymers were prepared in accordance with the polymerization method of Example I using 0.20 ml of zirconium acetyl acetonate catalyst (5000 : 1 monomer to catalyst ratio) and a polymerization temperature of 90° C. Polymer properties were as follows:

I.V.: 0.65
Tg: −19° C
Tm: 109° C
Crystallinity: 35%

EXAMPLE IV

The method of Example III was repeated using 0.50 ml of zirconium acetylacetonate catalyst. (2000 : 1 monomer to catalyst ratio). Polymer properties were as follows:

I.V.: 0.59
Tg: −17° C
Tm: 111° C
Crystallinity: 44%

EXAMPLE V

The method of Example I was repeated at a monomer to catalyst ratio of 4000 : 1 and with a polymerization reaction of three days at 80° C. The resulting polymer had an inherent viscosity of 0.86 and crystallinity of 30 percent. Fibers extruded from the polymer and drawn 6x at 87° C had a diameter of 9 mils, a straight tensile strength of 65,100 psi, elongation of 47.6%, and knot strength of 46,400 psi.

EXAMPLE VI

The method of Example I was repeated using tetraoctylene glycol titanate as the polymerization catalyst. The monomer to catalyst ratio was 12,300 : 1 based on titanium content, and the polymerization reaction was maintained at 80° C for six days. The resulting polymer had an inherent viscosity of 0.86 and a crystallinity of 33 percent. Extruded filaments drawn 6x at 83° C had a diameter of 11 mils, a tensile strength of 55,600 psi, a dry knot strength of 48,800 psi, and a Young's modulus of 167,000 psi.

EXAMPLE VII

Two lots of polydioxanone were prepared according to the method of Example VI using a monomer to catalyst ratio of 26,700 : 1 and with a polymerization reaction of six days and 12 days. The resulting polymers had inherent viscosities of 0.81 and 0.84 respectively. The polymers were combined and extruded into fiber which, after drawing 6x, had the following physical properties.

Fiber Diameter: 9 mils
Tensile Strength: 70,600 psi
Elongation: 46.3
Dry Knot Strength: 50,300 psi

The monofilament fibers had a high degree of softness and pliability.

EXAMPLE VIII

In Vivo Absorption

Two 2 cm segments of monofilament fiber from Example I having a diameter corresponding to size 2-0 suture were implanted aseptically into the left gluteal muscles of 24 female Long Evans rats. The implant sites were recovered after periods of 60, 90, 120 and 180 days and examined microscopically to determine the extent of absorption.

After 60 days the suture cross sections were still transparent and intact. The tissue reactions were slight and most sutures were encapsulated with fibrous tissue. The sutures at this period remained birefringent under polarized light.

At 90 days the sutures were becoming translucent and had lost some of their birefringent properties. A few of the suture cross sections stained pink (eosinophilic) around the periphery and the edges were indistinct, indicating the onset of absorption. The tissue reactions generally consisted of a fibrous capsule and a layer of macrophages interposed between it and the suture surface.

At 120 days the sutures were translucent, most cross sections had taken on an eosinophilic stain, and the sutures appeared to be in the process of active absorption. The tissue reactions consisted of an outer layer of fibroblasts with an interface of macrophages several cell layers thick. Absorption at 120 days was estimated to be approximately 70 percent complete.

At 180 days, absorption of the suture was substantially complete. The incision healed with minimal adverse tissue reaction.

EXAMPLE IX

In Vivo Strength Retention

Segments of the sutures of several Examples were implanted in the posterior dorsal subcutis of female Long Evans rats for periods of 14, 21 and 28 days. The

sutures were recovered at the designated periods and tested for straight tensile strength with the following results.

Test	Fiber	Implantation Time Days	Tensile Strength Pounds	Strength Retention %
a)	EX. I -	0	3.37	
		14	1.46	43.4
		21	1.14	33.8
		28	—	—
b)	EX. I - (Sterilized)[1]	0	3.08	
		14	1.16	37.6
		21	0.97	31.4
		28	0.70	22.9
c)	EX. VI - (Unannealed)	0	3.47	
		14	2.27	65.3
		21	1.62	46.7
		28	1.53	44.1
d)	EX. VI - (Annealed)[2]	0	6.47	
		14	5.39	83.3
		21	4.87	75.3
		28	4.30	66.5
e)	EX. VI - (Annealed)[2,3]	0	3.82	
		14	2.07	54.0
		21	1.36	35.5
		28	0.68	17.8
f)	EX. V - (Sterilized)[1]	0	4.05	
		14	2.77	68.4
		21	2.40	59.3
		28	2.15	53.2
g)	EX. V - (Sterilized)[3]	0	3.45	
		14	2.11	61.3
		21	1.36	39.3
		28	0.92	26.6

[1]Sterilzed with ethylene oxide at 30° C.
[2]Annealed under nitrogen 24 hours at 65° C.
[3]Sterilized with cobalt 60.

EXAMPLE X

Small quantities of polydioxanone polymer were prepared in accordance with the general method of Example I using chromatographically pure p-dioxanone monomer and diethyl zinc and tetraoctylene glycol titanate as catalysts. Polymer prepared with diethyl zinc catalyst at a monomer to catalyst ratio of 4,000 and with a polymerization reaction of three days at 80° C had an inherent viscosity of 1.18. Polymer prepared with tetraoctylene glycol titanate catalyst at a monomer to catalyst ratio of 12,250 and with a polymerization reaction of 6 days at 80° C had an inherent viscosity of 1.15. A second batch of high purity p-dioxanone monomer twice distilled in an annular still under a vacuum of 0.10–0.15 mm Hg was polymerized in the presence of tetraoctylene glycol titanate catalyst at a monomer to catalyst ratio of 13,300 and at 80° C for 6 days. The resulting polymer had an inherent viscosity of 2.26.

EXAMPLE XI

Preparation of Methyl-p-Dioxanone

Following the general procedure of Example I,, metallic sodium was dissolved in a large excess of 1,2-propane diol and chloroacetic acid was added at 110°–115° C. Excess diol was removed by distillation and the sodium salt of the hydroxy acid converted to free acid by the addition of water and hydrochloric acid. Sodium chloride was precipitated by the addition of ethanol and removed by filtration. The resulting product was distilled in the presence of M_gCO_3 to remove excess alcohol and water and to recover crude methyl dioxanone monomer as a distillate at 196° to 202° C. After purification, the monomer can be polymerized and extruded to form fibers suitable for use as absorbable sutures as described in Example I.

EXAMPLE XII

Preparation of Dimethyl-p-Dioxanone

The procedure of Example XI was repeated reacting metallic sodium with 2,3-butanediol and choroacetic acid at about 130° C. Crude dimethyl dioxanone monomer was recovered from the distillation at 190° to 213° C. After purification the monomer can be polymerized and extruded to form fibers suitable for use as absorbable sutures as described in Example I.

EXAMPLE XIII

Preparation of 1,4-dioxepan-2-one

The procedure of Example VI was repeated reacting metallic sodium with 1,3-propane diol and chloroacetic acid. Crude 1,4-dioxepan-2-one monomer was recovered from the distillation at 300° to 310° C. After purification, the monomer can be polymerized and extruded to form fibers suitable for use as absorbable sutures as described in Example I.

We have discovered that exceptionally high purity of p-dioxanone monomer is required to obtain polymers having a sufficiently high inherent viscosity to yield strong fibers upon extrusion. In general, the monomers are purified to 99+% by distillation and recrystallization prior to polymerization, and the resulting polymers have an inherent viscosity of at least about 0.50, and preferably 0.80 or higher measured as above described. As illustrated in Example X, polymers prepared from highly purified dioxanone have inherent viscosities well in excess of 1.10.

Drawn fibers of polydioxanone possess an unique combination of desirable properties. In particular, the monofilament fibers combine high tensile strength and knot strength with a pliability not to be found in any previous absorbable suture material, natural or synthetic. For example, the Young's modulus of the polydioxanone fiber of Example VI was 167,200 psi. In comparison, the Young's modulus for monofilament polyglycolide fibers and for 90/10 glycolide/lactide copolymer fibers is about 1 - 2 million psi, while that for moist catgut is about 350,000 psi. The low Young's modulus of polydioxanone makes this fiber particularly well suited for use as an absorbable monfilament suture, whereas prior synthetic absorbable sutures have largely been limited to braided, multifilament constructions which tend to be softer and more flexible than corresponding sizes of monofilament material. Monofilamented sutures are, of course, preferred for use in many surgical applications such as in ophthalmic procedures where smoothness of the suture surface is of particular importance.

The polymers of p-dioxanone of the present invention are also unique as compared with prior synthetic absorbable materials in that the sutures of these polymers can be sterilized by cobalt 60 radiation as well as by ethylene oxide. As illustrated in Example IX, while cobalt 60 sterilization results in some reduction in fiber strength and some increase in the in vivo rato of strength loss, the sterilized fiber nevertheless retains sufficient strength initially and for 28 days in vivo to make the fiber suitable for use in surgical procedures.

While the preceding examples have been directed to the preparation of homopolymers of p-dioxanone, methyl dioxanone, dimethyl dioxanone, and 1,4-dioxepan-2-one, these examples are for purposes of illustration only and are not limiting of the invention. Mixtures

of these polymers, copolymers of two or more of the above enumerated monomers, and copolymers of these monomers with up to about 50% by weight of other copolymerizable monomers which produce non-toxic and absorbable polymers are likewise included within the present invention. For example, such copolymers of dioxanone with lactide and/or glycolide are useful in the preparation of absorbable sutures, and the physical and chemical properties of such sutures such as strength, stiffness, and rate of absorption can be controlled by varying the relative propertions of the monomer constituents. In addition, the copolymers may be prepared by random, block or graft polymerization techniques in order to obtain particular combinations of compositions and physical and chemical properties. In certain applications where the rate of absorption of polydioxanone is less than desired, copolymers of dioxanone with from about 5 to 25 percent or more glycolide having a faster rate of absorption may be preferred.

It is to be understood that inert additives such as coloring materials and plasticizers can be incorporated in the sutures. Any of a variety of plasticizers such as, for instance, glyceryl triacetate, ethyl benzoate, diethyl phthalate, dibutyl phthalate and bis 2-methoxyethyl phthalate can be used if desired. The amount of plasticizer may vary from 1 to about 20 percent or more based on the weight of the polymer. Not only does the plasticizer render the filaments even more pliable, but it also helps in spinning. As used herein, the term "inert" means materials that are chemically inert to the polymer, and biologically inert to living tissue, i.e., do not cause any of the adverse effects previously discussed.

Filaments of the present invention are adversely affected by moisture and are accordingly preferably packaged in a substantially moisture free environment and in hermetically sealed packages, a preferred form of which is shown in FIG. 2. In FIG. 2, there is shown a suture package 14 having disposed therein a coil of suture 12, one end of which is attached to needle 13. The needle and suture are positioned within a cavity 16 that is evacuated or filled with a dry atmosphere such as air or nitrogen. The package is fabricated of two sheets of aluminum foil or an aluminum foil-plastic laminate and heat sealed or bonded with adhesive at the skirt 16 to hermetically seal the cavity and isolate the contents of the package from the external atmosphere.

Filaments of the present invention may be used as monofilament or multifilament sutures, or may be woven, braided, or knitted either alone or in combination with absorbable fibers such as polyglycolide or poly (lactide-co-glycolide), or with non-absorbable fibers such as nylon, polypropylene, polyethyleneterephthalate, or polytetrafluoroethylene to form multifilament sutures and tubular structures having use in the surgical repair of arteries, veins, ducts, esophagi and the like.

Multifilament yarns that contain polymer filaments of the present invention together with nonabsorbable filaments are illustrated in FIG. 4 wherein the nonabsorbable fiber is represented by the hatched fiber cross section 19. In FIG. 4, the fibers 20 are extruded from homopolymer or copolymer compositions of the present invention as described above. The relative proportions of absorbable filaments 20 and nonabsorbable filaments 19 may be varied to obtain the absorption characteristic desired in the woven fabric or tubular implants. Methods of weaving and crimping vascular prostheses are described in U.S. Pat. 3,096,560.

Composite fabrics of absorbable and nonabsorbable materials fashioned by textile processes including weaving, knitting, and fabricating by the nonwoven felting of fibers are described in U.S. Pat. No. 3,108,357 and U.S. Pat. No. 3,463,158. Similar techniques may be used in the manufacture of surgical aids wherein nonabsorbable fibers are combined with absorbable fibers composed of the polymers of this invention. The surgical utility of "bicomponent filaments" containing absorbable and nonabsorbable components is described in U.S. Pat. No. 3,463,158, the teaching of which is incorporated herein by reference. Monofilaments of the polymers of the present invention may be woven or knitted to form an absorbable fabric having the structure illustrated in FIG. 5, useful surgically in hernia repair and in supporting damaged liver, kidney, and other internal organs.

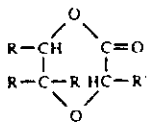
The products of the invention are useful in surgical applications where an absorbable aid or support is required, as for example, in the formation of surgical mesh, absorbable staples, artifical tendons, or cartilage material, and in other uses where a temporary aid during healing is needed. They may also be used to advantage in repairing hernias and in anchoring organs which have become loose.

The polymers of the present invention are also useful in the manufacture of cast films and other solid surgical aids such a scleral buckling prostheses. Thus, cylindrical pins, screws as illustrated in FIG. 3, reinforcing plates, etc., may be machined from the cast polymer having in vivo absorption characteristics depending upon the polymer composition and molecular weight.

Many different embodiments of this invention will be apparent to those skilled in the art and may be made without departing from the spirit and scope thereof. It is accordingly understood that this invention is not limited to the specific embodiments thereof except as defined in the appended claims.

We claim:

1. A sterile, synthetic absorbable suture comprising oriented fiber of a polymer of a monomer having the formula:



wherein R' and R are individually hydrogen, methyl or ethyl, said suture being dry to the extent of being substantially free of moisture, and characterized by a Young's modulus of less than about 600,000 psi with a correspondingly high degree of softness and flexibility, an initial straight tensile and knot strength of at least about 40,000 psi and 30,000 psi respectively, and substantially complete absorption in vivo within about 180 days.

2. A suture of claim 1 wherein R and R' are hydrogen and the monomer is p-dioxanone.

3. A suture of claim 2 wherein said polymer is characterized by an inherent viscosity greater than about 0.50 measured as 0.1% solution of polymer in tetrachloroethane at 25° C.

4. A suture of claim 3 comprising a homopolymer of p-dioxanone.

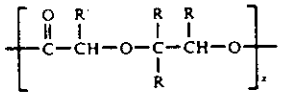
5. A suture of claim 1 comprising a polymer of methyl-p-dioxanone.

6. A suture of claim 1 comprising a polymer of dimethyl-p-dioxanone.

7. A suture of claim 1 comprising a copolymer of more than 50% by weight p-dioxanone and less than 50% by weight of at least one other monomer copolymerizable with p-dioxanone to an absorbable polymer.

8. A suture of claim 7 wherein said copolymer is of p-dioxanone and glycolide or lactide.

9. A sterile synthetic absorbable suture comprising oriented fiber of a polymer having units of the formula:



wherein R' and R are individually hydrogen, methyl, or ethyl and x is the degree of polymerization resulting in a fiber forming polymer, said suture being dry to the extent of being substantially free of moisture, and characterized by a Young's modulus of less than about 600,000 psi with a correspondingly high degree of softness and flexibility, an initial straight tensile and knot strenght of at least about 40,000 psi and 30,000 psi respectively, and substantially complete absorption in vivo within about 180 days.

10. A suture of claim 9 wherein said polymer is a homopolymer of p-dioxanone having an inherent viscosity of at least 0.50 in a 0.1% solution of tetrachloroethane at 25° C.

11. A suture of claim 10 wherein the inherent viscosity of said polymer is at least 0.80.

12. A suture of claim 9 wherein said polymer is a copolymer of more than 50% by weight p-dioxanone with less than 50% by weight of at least one other monomer copolymerizable to an absorbable polymer.

13. A suture of claim 12 wherein said polymer is a copolymer of p-dioxanone and lactide or glycolide.

14. A suture of claim 9 wherein said polymer is a homopolymer of methyl-p-dioxanone or copolymer of more than 50% by weight methyl-p-dioxanone with less than 50% by weight of at least one other monomer copolymerizable to an absorbable polymer.

15. A suture of claim 9 wherein said polymer is a homopolymer of dimethyl-p-dioxanone or copolymer of more than 50% by weight dimethyl-p-dioxanone with less than 50% by weight of at least one other monomer copolymerizable to an absorbable polymer.

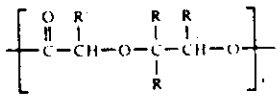
16. A suture of claim 1 having a surgical needle attached to at least one end thereof.

17. A needle and suture combination of claim 16 packaged in a sterile and dry environment within a hermetically sealed and substantially moisture impervious container.

18. A suture of claim 9 having a surgical needle attached to at least one end thereof.

19. A needle and suture combination of claim 18 packaged in a sterile and dry environment within a hermetically sealed and substantially moisture impervious container.

20. A surgical prosthesis comprising a fabric manufactured at least in part from synthetic absorbable fibers of a polymer having units of the formula:



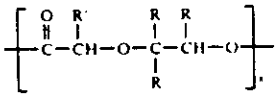
wherein R' and R are individually hydrogen, methyl, or ethyl and x is the degree of polymerization resulting in a fiber forming polymer, said fibers being dry to the extent of being substantially free of moisture, and characterized by a Young's modulus of less than about 600,000 psi with a correspondingly high degree of softness and flexibility, an initial straight tensile and knot strength of at least about 40,000 psi and 30,000 psi respectively, and substantially complete absorption in vivo within about 180 days.

21. A surgical prosthesis of claim 20 wherein said polymer is a homopolymer of p-dioxanone or a copolymer of more than 50% by weight p-dioxanone with less than 50% by weight of at least one other monomer copolymerizable to an absorbable polymer.

22. A surgical prosthesis of claim 20 wherein said polymer is a homopolymer of methyl-p-dioxanone or a copolymer of more than 50% by weight methyl-p-dioxanone with less than 50% by weight of at least one other monomer copolymerizable to an absorbable polymer.

23. A surgical prosthesis of claim 20 wherein said polymer is a homopolymer of dimethyl-p-dioxanone or a copolymer of more than 50% by weight dimethyl-p-dioxanone with less than 50% by weight of at least one other monomer copolymerizable to an absorbable polymer.

24. A surgical prosthesis comprising a solid surgical aid formed from an absorbable polymer having units of the formula:



wherein R' and R are individually hydrogen, methyl, or ethyl and x is the degree of polymerization resulting in a fiber forming polymer, said prosthesis being dry to the extent of being substantially free of moisture.

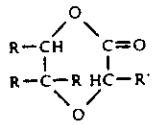
25. A surgical prosthesis of claim 24 wherein said polymer is a homopolymer of p-dioxanone having an inherent viscosity of at least 0.50 in a 0.1% solution of tetrachloroethane at 25° C.

26. A surgical prosthesis of claim 24 wherein said polymer is a copolymer of at least 50% by weight p-dioxanone with less than 50% by weight of at least one other monomer copolymerizable to an absorbable polymer.

27. A surgical prosthesis of claim 24 wherein said polymer is a homopolymer of methyl-p-dioxanone or acopolymer of more than 50% by weight methyl-p-dioxanone with less than 50% by weight of at least one other monomer copolymerizable to an absorbable polymer.

28. A surgical prosthesis of claim 24 wherein said polymer is a homopolymer of dimethyl-p-dioxanone or a copolymer of more than 50% by weight dimethyl-p-dioxanone with less than 50% by weight of at least one other monomer copolymerizable to an absorbable polymer.

29. A method of closing a wound in living tissue which comprises approximating the edges of the wound with a synthetic absorbable suture consisting of at least one filament of a polymer of a monomer having the formula:



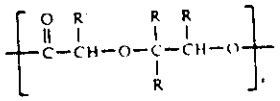
wherein R' and R are individually hydrogen, methyl or ethyl, said suture being at least partially embedded in the living tissue, and leaving said suture in said tissue until the embedded suture is absorbed during the healing process, said suture being characterized by a Young's modulus of less than about 600,000 psi with a correspondingly high degree of softness and flexibility, an initial straight tensile and knot strength of at least about 40,000 psi and 30,000 psi respectively, and substantially complete absorption in vivo within about 180 days.

30. A method of claim 29 wherein R and R' are hydrogen and the monomer is p-dioxanone.

31. A method of claim 29 wherein the monomer is methyl-p-dioxanone.

32. A method of claim 29 wherein the monomer is dimethyl-p-dioxanone.

33. A method of closing a wound in living tissue which comprises approximating the edge of the wound with a synthetic absorbable suture consisting of at least one filament of a polymer having units of the formula:



wherein R' and R are individually hydrogen, methyl or ethyl, and x is the degree of polymerization resulting in a fiber forming polymer, said suture being at least partially embedded in the living tissue, and leaving said suture in said tissue until the embedded suture is absorbed during the healing process, said suture being characterized by a Young's modulus of less than about 600,000 psi with a correspondingly high degree of softness and flexibility, an initial straight tensile and knot strength of at least about 40,000 psi and 30,000 psi respectively, and substantially complete absorption in vivo within about 180 days.

34. A method of claim 33 wherein said polymer is a homopolymer of p-dioxanone having an inherent viscosity of at least 0.50 in a 0.1 percent solution of tetrachloroethane at 25° C.

35. A method of claim 34 wherein the inherent viscosity of said polymer is at least 0.80.

36. A method of claim 33 wherein said polymer is a copolymer of more than 50% by weight p-dioxanone with less than 50% by weight of at least one other monomer copolymerizable to an absorbable polymer.

37. A method of claim 36 wherein said polymer is a copolymer of p-dioxanone and lactide or glycolide.

38. A method of claim 33 wherein said polymer is a homopolymer of methyl-p-dioxanone or a copolymer of more than 50% by weight methyl-p-dioxanone with less than 50% by weight of at least one other monomer copolymerizable to an absorbable polymer.

39. A method of claim 33 wherein said polymer is a homopolymer of dimethyl-p-dioxanone or a copolymer of more than 50% by weight dimethyl-p-dioxanone with less than 50% by weight of at least one other monomer copolymerizable to an absorbable polymer.

* * * * *

US005147400A

United States Patent [19]

Kaplan et al.

[11] Patent Number: 5,147,400

[45] Date of Patent: Sep. 15, 1992

[54] CONNECTIVE TISSUE PROSTHESIS

[75] Inventors: Donald S. Kaplan, Weston; John Kennedy, Stratford; Ross R. Muth, Brookfield, all of Conn.

[73] Assignee: United States Surgical Corporation, Norwalk, Conn.

[21] Appl. No.: 581,462

[22] Filed: Sep. 12, 1990

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 349,648, May 10, 1989, Pat. No. 4,990,158.

[51] Int. Cl.[5] A61F 2/08

[52] U.S. Cl. 623/13; 623/1; 623/11; 623/66

[58] Field of Search 623/1, 13, 11

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Primary Examiner—David Isabella
Assistant Examiner—Debra S. Brittingham
Attorney, Agent, or Firm—Thomas R. Bremer; Peter G. Dilworth; Rocco S. Barrese

[57] ABSTRACT

A semi-bioabsorbable connective tissue prosthesis, e.g., a replacement for the human anterior cruciate ligament, is provided whose stress-strain characteristics closely match those of the natural tissue.

58 Claims, 5 Drawing Sheets

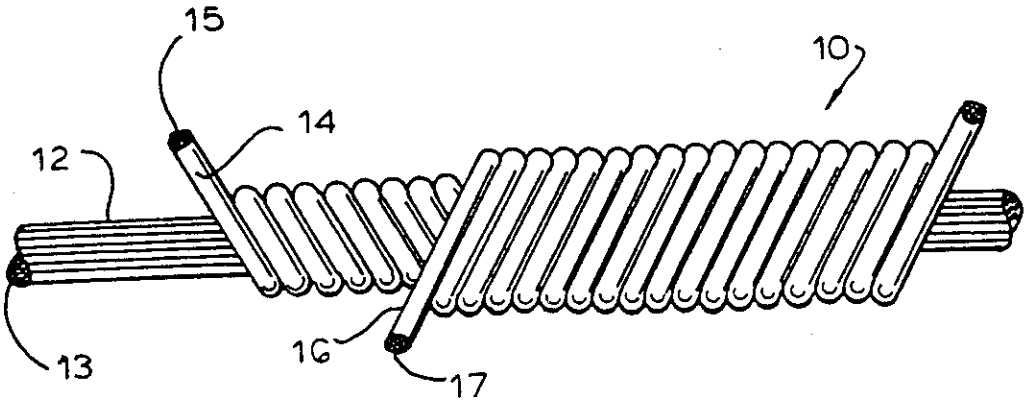
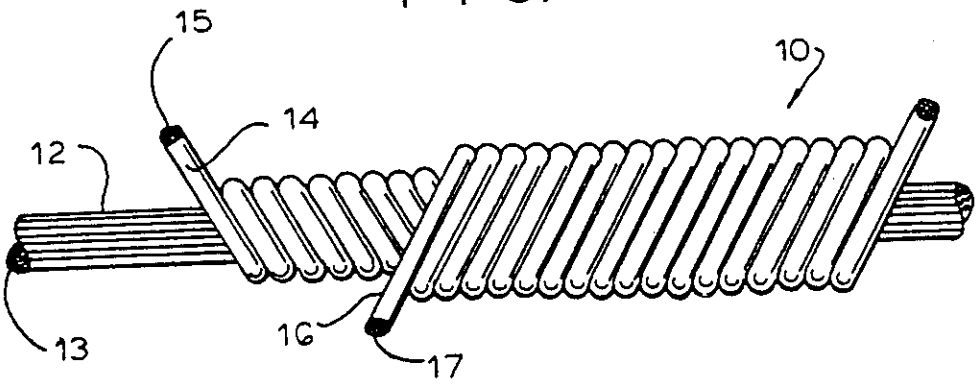


FIG. 1



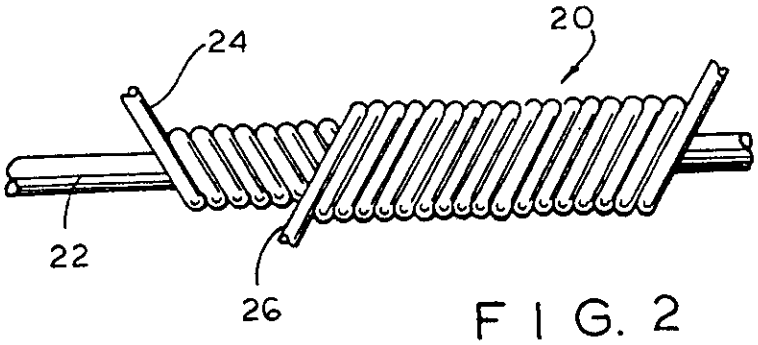


FIG. 2

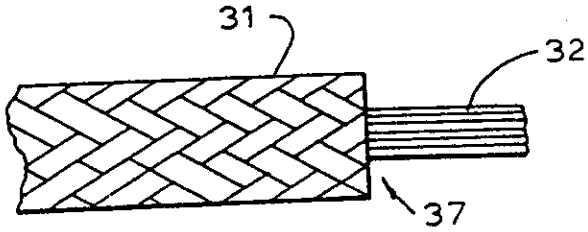
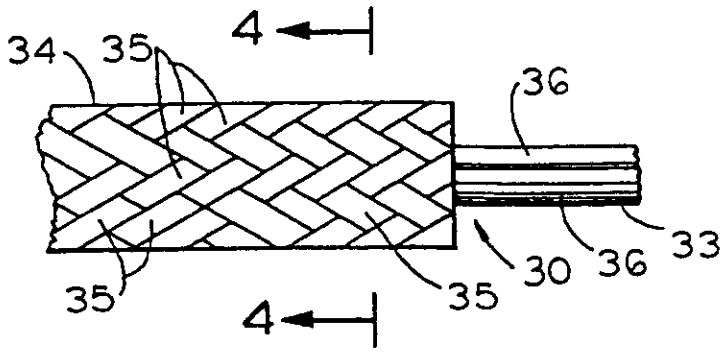


FIG. 5

FIG. 3



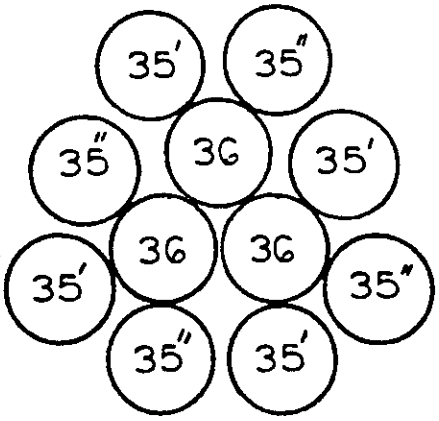
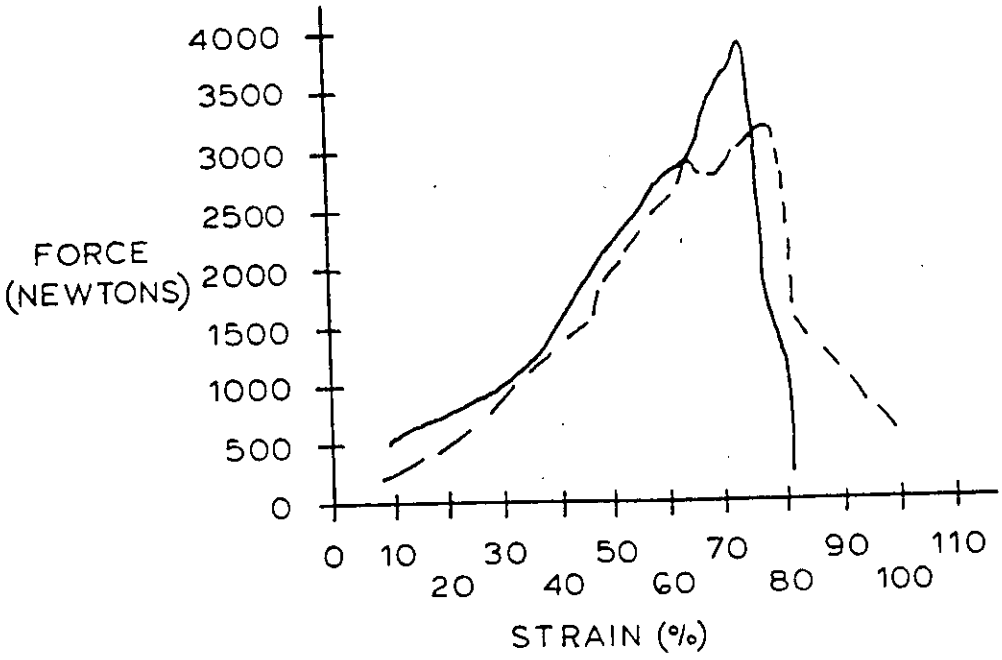


FIG. 4

FIG. 6



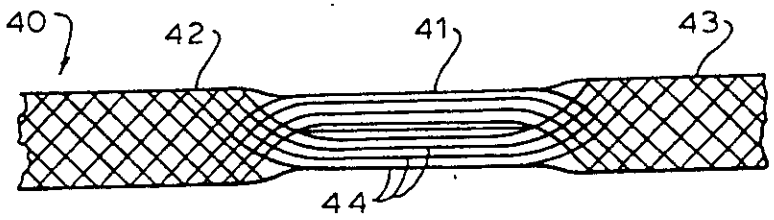


FIG. 7

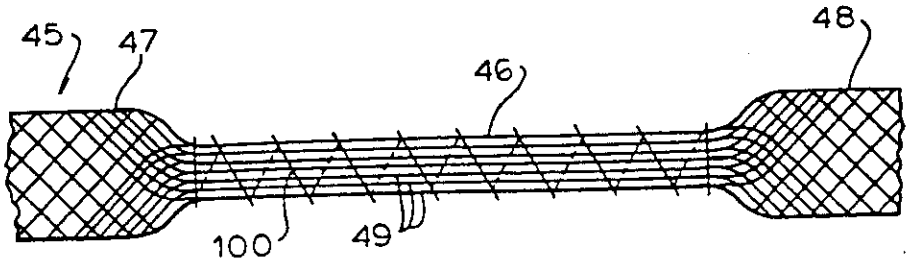


FIG. 8

FIG. 9

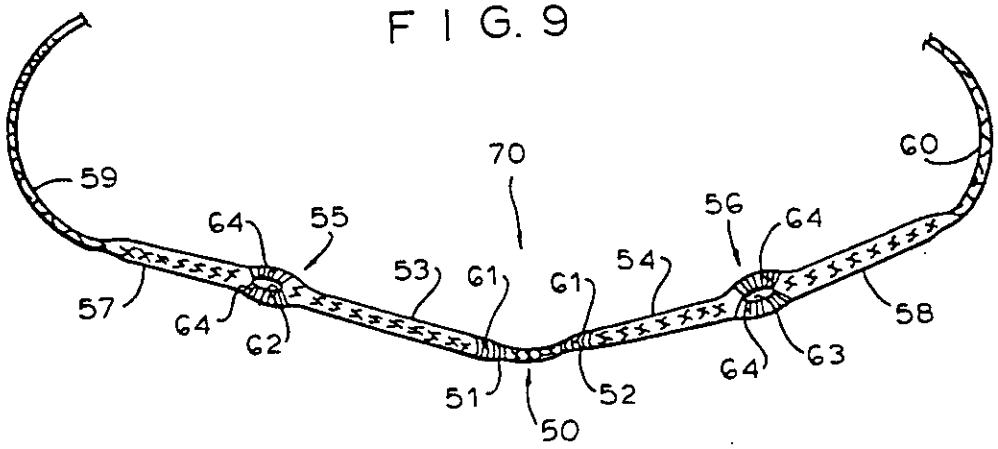


FIG. 10

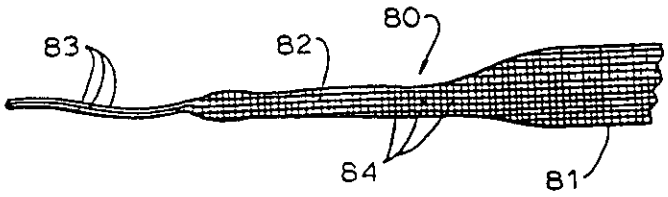
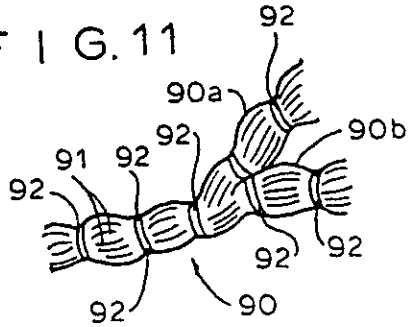


FIG. 11



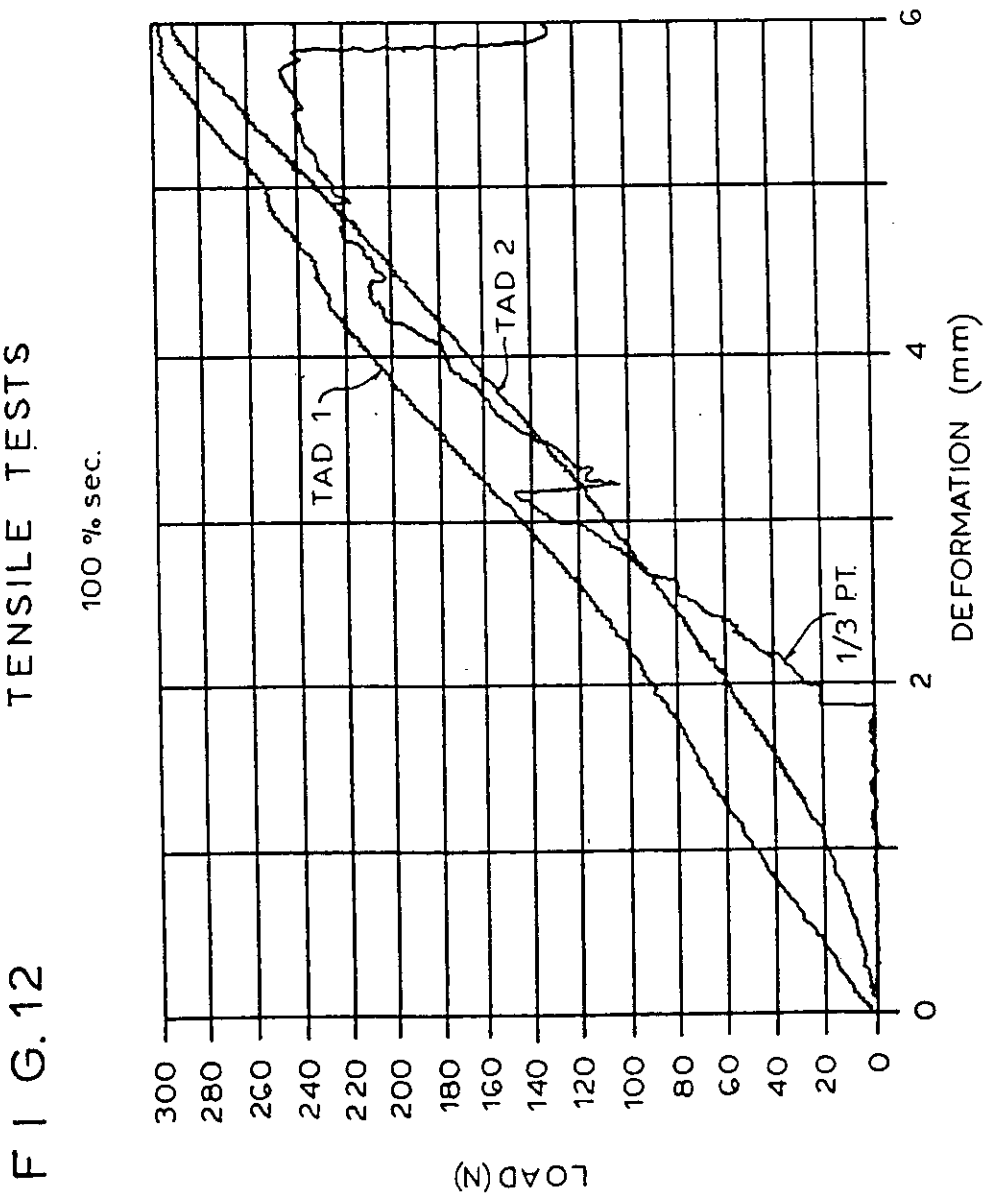

TENSILE TESTS
100 % sec.
TAD 1
TAD 2
1/3 PT.
DEFORMATION (mm)
LOAD (N)
0
2
4
6
0
20
40
60
80
100
120
140
160
180
200
220
240
260
280
300

FIG. 12

CONNECTIVE TISSUE PROSTHESIS

CROSS REFERENCE TO RELATED APPLICATION

The application is a continuation-in-part of commonly assigned, co-pending U.S. patent application Ser. No. 349,648, filed May 10, 1989, now U.S. Pat. No. 4,990,158.

BACKGROUND OF THE INVENTION

This invention relates to a connective tissue prosthesis and, in particular, to a biocompatible ligament or tendon prosthesis which closely approximates the biomechanical characteristics of the natural tissue to be replaced or augmented.

Numerous connective tissue materials and constructions have been proposed for use as temporary or permanent grafts in ligament and tendon repair. Feagin, Jr., Ed., *The Crucial Ligaments/Diagnosis and Treatment of Ligamentous Injuries About the Knee* (Churchhill Livingstone, N.Y., 1988) describes a number of partially bioabsorbable materials which have been investigated for use as ligament grafts. In Chapter 33 of this publication (Rodkey, "Laboratory Studies of Biodegradable materials for Cruciate Ligament Reconstruction"), it is reported that while a 100 percent biodegradable ligament fabricated from polyglycolic acid (PGA) was found to be safe, strong, well-tolerated and provided stability for the repaired anterior cruciate ligament in dogs, its complete resorption within five weeks makes it unsuitable for use in prostheses intended for humans since a human ligament prosthesis must provide support over a much longer period of time. It is further reported that a study in dogs of the intraarticular use of a partially biodegradable ligament prosthesis possessing a Dacron (i.e., DuPont's polyethylene terephthalate (PET)) and PGA core and a separate outer sleeve woven from PGA and Dacron of a different percentage of composition gave disappointing results.

U.S. Pat. Nos. 4,792,336 and 4,942,875 describe a surgical device for repairing or augmenting connective tissue and comprising a plurality of fibers, in which the majority of the fibers are in a direction essentially parallel to the length of the device and can be either 100 percent bioabsorbable or can contain a nonabsorbable component. Additionally, sleeve yarns consisting completely of absorbable material wrap around these axial or warp yarns.

Biomedical Business International Report No. 7041 (Second Revision, May 1986), "Orthopaedic and Diagnostic Devices", pages 5—5 to 5-12, identifies a variety of materials which have been used in the fabrication of prosthetic ligaments including carbon fiber, expanded Teflon (i.e., DuPont's polytetrafluoroethylene), a combination of silicone and PET, polypropylene, polyethylene, nickel-chromium alloy fibers individually enclosed in synthetic textile or natural silk, carbon material coated with gelatin, polyester combined with PET fibers, bovine tissues, and others.

Other disclosures of ligament and tendon repair devices are provided, inter alia, in U.S. Pat. Nos. 3,805,300; 4,187,558; 4,301,551; 4,483,023; 4,584,722; 4,610,688; 4,668,233; 4,775,380; 4,788,979; and PCT Patent Publication No. WO 89/01320.

Chapter 33 (page 540) of the Feagin, Jr. publication referred to above identifies the characteristics of an ideal ligament prosthesis as follows:

(1) it must be durable with adequate strength to withstand the extreme forces placed upon it, yet compliant enough to allow for repetitive motion without failure or excessive creep elongation;

(2) it must be tolerated by the host with no antigenic or carcinogenic reaction;

(3) if partially or completely biodegradable, the size of the individual fibers and the construction pattern must be appropriate to support and allow eventual reconstitution of the repaired structure with ingrowth of fibrous tissue that matures to normal or near normal collagen;

(4) it must tolerate sterilization and storage; and

(5) it should be easily implanted using surgical and potentially arthroscopic techniques.

The existence of so many different types of materials and devices for use in connective tissue repair, some of which have been identified above, bears testimony to the difficulty of meeting some, much less all, of the foregoing characteristics in a single prosthetic device.

SUMMARY OF THE INVENTION

It is a principal object of the invention to provide a semi-bioabsorbable or fully bioabsorbable connective tissue prosthesis, e.g., a ligament or tendon repair device, which exhibits the stress-strain properties of the natural tissue to be replaced or augmented.

It is a specific object of the invention to provide the foregoing connective tissue prosthesis as a structure formed from a composite yarn comprising a non-bioabsorbable core yarn surrounded by a bioabsorbable or semi-bioabsorbable cover or sheath yarn.

It is a further specific object of the invention to provide a connective tissue prosthesis formed from a composite yarn wherein an elastic core yarn is wrapped with a relatively inelastic, bioabsorbable or semi-bioabsorbable sheath yarn, so as to exhibit the stress-strain properties of natural tissue.

It is another specific object of the invention to provide a prosthetic replacement for a human anterior cruciate ligament which is based on the aforesaid structure, in particular, one fabricated from a yarn whose sheath yarn component is derived from a glycolide-lactide copolymer.

In keeping with these and other objects of the invention, there is provided a connective tissue prosthesis comprising:

(a) a core made up of a first biocompatible composite yarn extending in the lengthwise direction; and

(b) a sheath surrounding the core and fabricated from a second biocompatible yarn,

wherein the first composite yarn in the core (a) comprises a biocompatible, non-bioabsorbable core yarn component surrounded by a biocompatible, bioabsorbable or semi-bioabsorbable sheath yarn component.

The second biocompatible yarn forming the sheath (b) may be the same as, or different from, the first composite yarn which forms the core (a). More specifically, the second biocompatible yarn may also comprise a biocompatible, non-bioabsorbable core yarn component surrounded by a biocompatible, bioabsorbable or semibioabsorbable sheath yarn component.

Also in keeping with the above and other objects of the invention, a connective tissue prosthesis is provided which comprises a tubular component fabricated from

composite yarn, the yarn comprising a biocompatible, nonbioabsorbable core yarn component surrounded by a biocompatible, bioabsorbable or semi-bioabsorbable sheath yarn component.

The foregoing connective tissue prostheses meet the Feagin, Jr. criteria, identified sucra, to a surprising degree. Due to elasticity of the composite yarn core component and relative inelasticity of the composite yarn sheath component, the stress-strain characteristics of the connective tissue prostheses closely match those of the natural tissue which they replace and their resorption properties can be calibrated to maintain the functionality of the prostheses throughout the entire period of the tissue regeneration process. The prostheses of this invention are readily sterilizable, possess good storage stability when suitably protected from hydrolytic forces, and can be installed at a ligament, tendon, vascular, or tracheal repair site employing known surgical reconstruction techniques.

BRIEF DESCRIPTION OF THE DRAWINGS

FIGS. 1 and 2 are enlarged isometric views of composite yarns which are utilized in the construction of the connective tissue prosthesis herein;

FIG. 3 is an enlarged isometric view of an alternative composite yarn utilized in the construction of the connective tissue prosthesis herein;

FIG. 4 is a schematic, cross-sectional view along line 4—4 of FIG. 3;

FIG. 5 represents a section of a ligament prosthesis manufactured from the composite yarn of FIG. 1 and suitable for use in the surgical reconstruction of the human anterior cruciate ligament;

FIG. 6 is a plot of experimental data showing the stress-strain characteristics of the prosthesis of FIG. 5 compared with the stress-strain characteristics of a natural ligament as reported in the literature;

FIG. 7 represents a section of a tubular ligament prosthesis manufactured from the composite yarn of the present invention and having an unbraided center section;

FIG. 8 represents a section of a tubular ligament prosthesis similar to FIG. 7 and additionally having the unbraided center section helically wrapped with a yarn;

FIG. 9 represents a section of a braided prosthesis manufactured from composite yarn of the present invention and modified in various fashion over the length thereof;

FIG. 10 represents a section of a tubular braided prosthesis manufactured from composite yarn of the present invention and provided with threading means;

FIG. 11 represents a section of a prosthesis manufactured from composite yarn of the present invention in which the prosthesis is branched; and

FIG. 12 is a plot of experimental data showing the stress-strain characteristics of the prosthesis of FIG. 7 compared with a canine patellar tendon.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

As shown in FIG. 1, composite yarn 10 comprises a core yarn component 12 made up of a multiplicity of individual biocompatible, essentially non-bioabsorbable and preferably elastic filaments 13, advantageously provided with a slight to moderate twist, and a sheath yarn component 14 made up of a multiplicity of individual biocompatible, bioabsorbable or semi-bioabsorbable and preferably relatively inelastic filaments 15 wound in a first direction around the core and an external multifilamentous sheath yarn component 16, also made up of individual biocompatible, bioabsorbable or semi-bioabsorbable and preferably relatively inelastic filaments 17, wound in a second and opposite direction around sheath yarn component 14. For example, multifilamentous sheath yarn component 16 may comprise both absorbable and non-absorbable filaments 17. Generally, the filaments 13 of core yarn component 12 are substantially parallel.

Non-bioabsorbable core yarn component 12 functions to impart elasticity to composite yarn 10 and acts as a scaffolding during and after absorption of the bioabsorbable sheath. Bioabsorbable sheath yarn components 14 and 16 function to provide the composite yarn with relative inelasticity, tensile strength, and absorption characteristics which allow for desirable tissue ingrowth and incorporation of the composite yarn into the body structure. Sheath yarn components 14 and 16 each have a lengthwise axis which is non-perpendicular to the lengthwise axis of core component 12. While core yarn component 12 can be wrapped with a single layer of sheath yarn component, the illustrated arrangement of two layers of sheath yarn components 14 and 16 is generally preferred as this construction helps to give composite yarn 10 a balanced structure which resists crimping or kinking when used in the manufacture of a prosthesis such as shown in FIGS. 5 and 7-11.

Where, as shown in the embodiment of FIG. 1, at least two sheath yarn components are employed in the construction of the composite yarn, the composition, number and denier of the individual filaments, and braiding (if any) of these yarn components as well as their relative rates of bioabsorption can differ. For example, non-absorbable filaments may be combined with absorbable filaments to provide one or more semi-absorbable sheath yarn components. This capability for differential absorption can be advantageously exploited in a connective tissue prosthetic device in which the outermost sheath yarn component is absorbed by the body at a faster rate than the underlying sheath yarn component, or vice versa. thus resulting in a staged absorption of the sheath components of the composite yarn.

Core yarn component 12 must be essentially non-bioabsorbable, i.e., it must resist degradation when, as part of the connective tissue prosthesis of this invention, it is implanted in a body. The term "non-bioabsorbable" as used herein applies to materials which permanently remain within the body or at least remain in the body for a relatively long period of time, e.g., at least about two years. It is preferred to employ a core yarn material which is also elastic, i.e, a polymeric material which in filamentous form exhibits a relatively high degree of reversible extensibility, e.g., an elongation at break of at least about 30 percent, preferably at least about 40 percent and more preferably at least about 50 percent. Fiber-forming polymers which are both non-bioabsorbable and elastic, and as such preferred for use as the core yarn component herein, include fiber-forming polyolefins such as polyethylene homopolymers, polypropylene homopolymers, ethylene propylene copolymers, ethylene propylene terpolymers, etc., fluorinated hydrocarbons, fluorosilicones, isobutylenes, isoprenes, polyacrylates, polybutadienes, polyurethanes, polyether-polyester copolymers, and the like. Hytrel (DuPont), a family of copolyester elastomers based on (soft) polyether segments and (hard) polyester segments, and span-

dex, an elastomeric segmented polyurethane, provide especially good results.

Hytrel is manufactured in various commercial grades by DuPont, such as Hytrel 4056, 5526, 5556 and 7246. Hytrel 5556 is especially suitable as the core component 12 of the composite yarn 10 when used to form a vascular graft, while Hytrel 7246 is well-suited for the core component 12 of the composite yarn 10 when used to form a ligament prosthesis or tendon augmentation device.

Several properties of the various Hytrel grades are presented in the table below:

	Hytrel Grade No. (Injection Molded at 23° C. for Testing)			
	4056	5526	5556	7246
Hardness in durometer points (ASTM Test No. D2240)	40	55	55	72
Flexural Modulus (ASTM Test No. D790)				
at −40° C. in MPa	155	930	930	2,410
at −40° F. in psi	22,500	135,000	135,000	350,000
at 23° C. in MPa	55	207	207	518
at 73° F. in psi	8,000	30,000	30,000	75,000
at 100° C. in MPa	27	110	110	207
at 212° F. in psi	3,900	16,000	16,000	30,000
ASTM Test No. D638				
[i]Tensile Strength at Break,				
MPa	28.0	40.0	40.0	45.8
psi	4050	5800	5800	6650
[i]Elongation at Break, %	550	500	500	350
[ii]Tensile Stress at 5% Strain,				
MPa	2.4	6.9	6.9	14.0
psi	350	1,000	1,000	2,025
[ii]Tensile Stress at 10% Strain,				
Mpa	3.6	10.3	10.3	20.0
psi	525	1,500	1,500	2,900
Izod Impact (Notched) (ASTM Test No. D256, Method A)				
at −40° C. in J/cm	No Break	No Break	No Break	0.4
at −40° F. in ft-lbf/in	No Break	No Break	No Break	0.8
at 23° C. in J/cm	No Break	No Break	No Break	2.1
at 73° F. in ft-lbf/in.	No Break	No Break	No Break	3.9
Resistance to Flex Cut Growth, Ross (Pierced), in Cycles to 100% cut growth (ASTM. Test No. D1052)	$>1 \times 10^6$	$>5 \times 10^5$	$>5 \times 10^5$	—
[iii]Initial Tear Resistance, Die C (ASTM Test No. D1004),				
in kN/m	101	158	158	200
in lbf/in	580	900	900	1,146
Melt Flow Rate in g/10 min. (ASTM Test No. D1238)	5.3	18	7.0	12.5
Test Conditions: Temperature, °C./Load, Kg	190/2.16	220/2.16	220/2.16	240/2.16
[iv]Melting Point (ASTM Test No. D3418)				
in °C.	148	202	202	219
in °F.	298	396	396	426
Vicat Softening Point (ASTM Test No. D1525)				
in °C.	108	180	180	207
in °F.	226	356	356	405
Specific Gravity (ASTM Test No. D792)	1.16	1.20	1.20	1.25
Water Absorption, 24 hr. in % (ASTM Test No. D570)	0.6	0.5	0.5	0.3

[i]head speed 50 mm/min. or 2 in/min
[ii]head speed 25 mm/min or 1 in/min.
[iii]specimens 1.9 mm or 0.075 in. thick.
[iv]differential scanning calorimeter (DSC), peak of endotherm

Corresponding properties of other grades of Hytrel are available from DuPont.

If desired, the core yarn component can be provided with a nonabsorbable hydrophilic coating to improve its wettability by body fluids, e.g., synovial fluid. Hydrophilic coatings which are suitable for this purpose include polymeric materials such as the sparingly cross-linked poly(hydroxyethyl methacrylate) hydrogels disclosed in U.S. Pat. Nos. 2,976,576 and 3,220,960; hydrogels based on cross-linked polymers of n-vinyl lactams and alkyl acrylates as disclosed in U.S. Pat. No. 3,532,679; graft copolymers of hydroxyalkyl methacrylate and polyvinylpyrrolidone disclosed in U.S. Pat. No. 3,621,079, and many others.

Fiber-forming materials which are relatively inelastic are suitable for providing the sheath yarn component of composite yarn 10 provided such materials are fairly rapidly bioabsorbed by the body, e.g., exhibiting a loss of tensile strength in from about 2 to about 26 weeks and total absorption within from about two to about fifty

two weeks. It is to be understood, however, that the expression "relatively inelastic" does not preclude the presence of some minor degree of elasticity in the sheath yarn component, merely that it excludes a degree of elastic behavior as described in connection with the preferred type of core yarn component.

The sheath yarn component can be woven, braided or knitted in whole or in part and will ordinarily possess a relatively high tensile strength, e.g., a straight tensile strength of at least about 30,000 p.s.i., preferably at least about 60,000 p.s.i. and more preferably at least about 90,000 p.s.i.

Bioabsorbable, relatively inelastic fiber-forming polymers and polymer blends from which the sheath yarn component herein can be formed include those derived at least in part from such monomers as glycolic acid, glycolide, lactic acid, lactide, p-dioxanone, trimethylene carbonate, e-caprolactone, hydroxycaproic acid, etc., and various combinations of these and related monomers as disclosed, e.g., in U.S. Pat. Nos. 2,668,162; 2,703,316; 2,758,987; 3,225,766; 3,297,033; 3,422,181; 3,531,561; 3,565,077; 3,565,869; 3,620,218; 3,626,948; 3,636,956; 3,736,646; 3,772,420; 3,773,919; 3,792,010; 3,797,499; 3,839,297; 3,867,190; 3,878,284; 3,982,543; 4,047,533; 4,052,988; 4,060,089; 4,137,921; 4,157,437; 4,234,775; 4,237,920; 4,300,565; 4,429,080; 4,441,496; 4,523,591; 4,546,152; 4,559,945; 4,643,191; 4,646,741; 4,653,497; and, 4,741,337; U.K. Patent No. 779,291; D. K. Gilding et al., "Biodegradable polymers for use in surgery—polyglycolide/poly(lactic acid) homo- and copolymers: 1", *Polymer*, Volume 20, pages 1459–1464 (1979), and D. F. Williams (ed.), *Biocompatibility of Clinical Implant Materials*, Vol. II, ch. 9: "Biodegradable Polymers" (1981).

Sheath yarn components manufactured from polymers of high lactide or glycolide content, e.g., those in which at least about 75 percent of the monomeric units are derived from either glycolide or lactide, are preferred for the construction of the composite yarn of this invention. Polymers of high glycolide content tend to be absorbed more quickly than those possessing a high lactide content. Accordingly, the glycolide-based polymers may be preferred for the manufacture of a sheath yarn component providing the outermost sheath yarn(s) in a multiple sheath yarn component construction, the underlying internal sheath yarn(s) being manufactured from the more slowly absorbable lactide-based polymers. An especially preferred lactide-glycolide copolymer for forming the sheath yarn component of the composite yarn contains from about 70 to about 90, and preferably from about 75 to about 85 mole percent lactide monomer with the balance being provided by the glycolide monomer. Thus, for example, a sheath yarn component formed from a lactide-glycolide copolymer based on 80 mole percent lactide-20 mole percent glycolide is especially advantageous for constructing the composite yarn, and ultimately, the connective tissue prosthesis, of the present invention. The sheath yarn component, which is preferably braided around the core yarn component, may comprise a plurality of bioabsorbable fibers in turn comprising at least two different chemical compositions.

The deniers of core yarn component **12** and sheath yarn components **14** and **16** are not especially critical and those of commercially available yarns such as Vicryl (a glycolide/lactide copolymer suture available from Ethicon) and Dexon (a polyglycolide suture available from American Cyanamid) are suitably employed. Preferably, the deniers are selected so as to provide a composite yarn having an overall denier of from about 40 to about 1200 and preferably from about 80 to about 500, the overall denier of the core and/or sheath yarn components being from about 20 to about 600 and preferably from about 40 to about 300. The deniers of individual filaments in the core and sheath yarn components of multifilamentous construction can vary widely, e.g., from about 0.2 to about 6.0 and preferably from about 0.4 to about 3.0. The base weight for a desired composite yarn will determine the size and weight of the component elements of the yarn. Composite yarn **10** possesses sufficient core material to impart, inter alia, a desired resiliency and sufficient sheath material to provide, inter alia. a desired tensile strength for a particular connective tissue prosthetic application. In general, the core component can represent from about 20 to about 80 percent, and preferably from about 30 to about 70 percent of the total weight of composite yarn **10**. Optimum core and sheath component weights will naturally vary depending on the specific application and can be readily determined in a given case based on the desired physical properties of the prosthetic device without undue experimentation.

Methods and apparatus for covering core yarn components with sheath yarn components are well known and need not be described here in detail. In general, the sheath yarn components are wrapped about the core yarn component on a covering machine which includes a hollow spindle with rotating yarn supply bobbins supported thereon. The elastic core yarn component is fed through the hollow spindle and the elastic sheath yarn components are withdrawn from the alternate direction rotating supply bobbins and wrapped about the core yarn component as it emerges from the hollow spindle. The core yarn component is preferably under a slight tension during the covering procedure and the sheath yarn components are laid down in a side-by-side array. The number of wraps per inch will depend on the denier of the sheath yarn components but should be sufficient to cause the sheath yarn components to lay close to the core yarn component when tension on the latter is relaxed.

As desired, the filaments which comprise a sheath yarn component can be provided with no twist or with varying degrees of twist. Where the yarns are twisted, it can be advantageous to balance or equalize the twist in the final composite yarn structure. Thus, for example, in the embodiment of composite yarn **10** in FIG. **1**, if sheath yarn component **14** has a given twist, sheath yarn component **16** should have an equivalent twist. Since sheath yarn components **14** and **16** are laid down in opposite directions, the twist in each of these yarn components will be neutralized in the final structure of the composite yarn. Similarly, sheath yarn components **14** and **16** are advantageously of about equal weight in order to provide further balance in the composite yarn.

The composite yarn **20** shown in FIG. **2** is similar to that of FIG. **1** except that core yarn component **22** constitutes a monofilament and internal and external sheath yarn components **24** and **26**, respectively, each constitutes a monofilament. In all other structural and compositional respects, composite yarn **20** can be like that of composite yarn **10**.

An alternative composite yarn **30** is illustrated in FIGS. **3** and **4**. Composite yarn **30** comprises a core yarn component **33** and a braided sheath yarn component **34**. As with core yarn components **12** and **22** of

FIGS. 1 and 2, core yarn component 33 is made up of one or more biocompatible, essentially non-bioabsorbable and preferably elastic filaments 36 which define the longitudinal axis of composite yarn 30. Braided sheath yarn component 34 comprises individual sheath yarn filaments or sheath yarn filament bundles 35 which traverse core yarn component 33 in a substantially conventional braided configuration to provide core yarn component 33 with a braided tubular external sheath 34. The individual sheath yarn filaments or sheath yarn filament bundles 35 are biocompatible, bioabsorbable or semi-bioabsorbable, and relatively inelastic. In a preferred embodiment of the present invention as illustrated in FIGS. 3 and 4, sheath yarn component 34 comprises sheath yarn filaments of different chemical composition. For example, a portion of the sheath yarn filaments 35', e.g., 30 to 70% by weight, may be formed of a bioabsorbable polymer exhibiting relatively slow bioabsorption, e.g., polylactide or a copolymer comprising a high lactide mole percentage, while the remainder of the sheath yarn filaments 35'' may be formed of a second bioabsorbable polymer which exhibits relatively fast bioabsorption, e.g., polyglycolide or a copolymer comprising a high glycolide mole percentage. Sheath yarn component 34 may also be fabricated from individual filaments having more than two different chemical compositions, one or more of which optionally being nonbioabsorbable.

In the embodiment illustrated in FIGS. 3 and 4, core yarn component 33 is preferably manufactured from Hytrel filaments 36 and has a denier of about 270, while sheath yarn component 34, which is braided on an eight carrier braider, has a denier of about 204, for a total denier of this composite yarn 30 of about 474.

FIG. 5 illustrates an anterior cruciate ligament prosthesis 37 manufactured from warp and filling composite yarns 10 of FIG. 1. Prosthesis 37 is constructed by constructing a sheath 31 about core 32 by weaving, braiding or knitting on a known or conventional loom. For example, the sheath may be braided about the core on a braiding machine which includes braider bobbins. Composite yarn forming the sheath may be wound onto an appropriate number of braider bobbins which are then loaded onto a carrier braider with the yarns on the bobbins then being braided and tied to form the sheath. The core (if one is required) can be pulled through the sheath, e.g. manually to form the prosthesis. In other words, the core will be at least partially surrounded by the sheath. Other prostheses illustrated herein can be manufactured in similar fashion. The sheath components of the individual composite yarns from which ligament prosthesis 30 is manufactured will erode over time due to their bioabsorption leaving only the nonabsorbable core component as a permanent or long term scaffold for new ligament tissue growth.

FIGS. 7-11 illustrate examples of other ligament prostheses which can be manufactured from the composite yarn of the present invention, e.g. as illustrated in FIGS. 1-3. More particularly, FIG. 7 illustrates a tubular ligament prosthesis or tendon augmentation device 40 having an unbraided center section 41 bounded by braided sections 42 and 43. The individual composite yarns 44 in the unbraided center section 41 can be drawn in generally parallel relationship, if required. The length of the unbraided center section 41 can vary, e.g., from about one or two inches up to about seven or eight inches. The unbraided center section 41 provides tensile strength and/or tissue ingrowth advantages.

Additionally, a tubular ligament prosthesis or tendon augmentation device 45 as illustrated in FIG. 8 can be manufactured from the composite yarn of the present invention. The prosthesis 45 is similar to the one illustrated in FIG. 7 and comprises an unbraided center section 46 bounded by braided sections 47 and 48. A helical wrap 100 is provided about the unbraided center section 46 to improve handling and manipulation of the unbraided section 46 during implantation, while absorption/degradation of the helical wrap 100 frees the individual yarns 49 of the center unbraided section 46 to provide the appropriate tensile strength and/or tissue ingrowth advantages. In this regard, the yarn forming the helical wrap 100 can be the composite yarn of FIGS. 1-3 or formed of a different kind of material, e.g. completely bioabsorbable or nonbioabsorbable material. The tubular ligament prostheses of FIGS. 7 and 8 are both constructed by braiding the end sections 42, 43 or 47, 48 in a known or conventional loom and, in the case of FIG. 8, additionally wrapping the helical yarn 100 about the center unbraided section 46, also with a known or conventional loom. The prostheses of FIGS. 7 and 8 are especially suitable as replacements for anterior cruciate ligaments.

FIG. 9 illustrates a braided prosthesis 70 which can be manufactured from the composite yarns of FIGS. 1-3 and which is also modified along the length thereof. More specifically, the prosthesis of FIG. 9 comprises a center region 50 bordered by first outer regions 51, 52, second outer regions 53, 54, third outer regions 55, 56, fourth outer regions 57, 58, and fifth outer regions 59, 60. The center region 50 comprises a sheath of braided composite yarn, e.g., as illustrated in FIGS. 1-3, about a core (not illustrated) also formed of composite yarn. First outer regions 51, 52 additionally comprise a wrapping 61 about the braided yarn, this wrapping 61 being formed of the same composite yarn as illustrated in FIGS. 1-3 or a different kind of material, e.g. a totally bioabsorbable or nonabsorbable material. This wrapping 61 serves to at least temporarily retain the sheath about the core.

The second outer regions 53, 54 also formed of tubular braided composite yarn as illustrated in FIGS. 1-3 with an appropriate core material (not illustrated) that forms a thicker core than any core present in center section 50 (the center section 50 can be coreless, if required). Third outer regions 55, 56 are divided as illustrated in FIG. 9 to form respective openings 62 and 63. This allows attachment means to be inserted through the respective openings to secure the ligament prosthesis 70 in place. As illustrated in FIG. 9, the sections 55, 56 around the openings 62 and 63 are also covered with wrapping 64 which is similar to the wrapping 61 covering regions 51 and 52.

Next, fourth outer regions 57 and 58 follow which are similar in structure and composition to second outer regions 53 and 54. Regions 57 and 58 narrow down into fifth outer regions 59 and 60 as illustrated in FIG. 9, which can be used, e.g. for threading the ligament prosthesis 70. All sections of prosthesis 70, including the various wrappings 61 and 64, can be fabricated together on a conventional known loom. Prosthesis 70 is especially suitable as a replacement for an anterior cruciate ligament.

FIG. 10 discloses a coreless prosthetic ligament 80 that can be prepared from the composite yarn illustrated in FIGS. 1-3. The coreless prosthetic ligament is braided with a wider central section 81, and a narrower

outer section from which unwoven yarns 83 extend to form a leading section to enhance threading of prosthetic ligament 80 upon implantation. Sheath yarns 84 of prosthetic ligament 80 can be woven, braided, or knitted on a conventional loom. Sheath sections 81 and 82 of ligament prostheses 80 are tubular, i.e. coreless. Prostheses 80 is also especially suitable as a replacement for an anterior cruciate ligament.

As illustrated in FIG. 11, a ligament prosthesis 90 can be prepared from composite yarns illustrated in Figs. 1-3 of the present invention which form a sheath about a supporting structure (not illustrated). This supporting structure can be a core formed from the composite yarns as described above, or it can be a single, integral member, formed of semi-bioabsorbable or non-bioabsorbable material forming a supporting base for yarns 91. This supporting structure, along with the bundle of yarns 91, can be divided into two branches 90*a* and 90*b*, with the yarns 91 of the prosthesis retained on the supporting structure or core at various points by fastening means 92 which can also be constituted by composite yarn of FIGS. 1-3 or by other kinds of material, e.g. totally bioabsorbable or nonabsorbable filaments. In this regard, the yarns 91 need just be bundled together without any interweaving, braiding or knitting, so long as the yarns 91 are securely held together on the core by the fastening means 92. Alternatively, yarns 92 can be woven, knitted, or braided about the core on a conventional loom to form branches 90*a* and 90*b*.

Other prosthetic structures which can be prepared with the composite yarn of the present invention are apparent to one of skill in the art in light of the disclosure herein.

It is within the scope of this invention to coat or impregnate the prosthesis with, or otherwise apply thereto, one or more materials which enhance its functionality, e.g., surgically useful substances, such as those which accelerate or beneficially modify the healing process when the prosthesis is applied to a graft site. So, for example, the prosthesis can be provided with a therapeutic agent which will be deposited at the grafted site. The therapeutic agent can be chosen for its antimicrobial properties, capability for promoting tissue repair or for specific indications such as thrombosis. Thus, for example, antimicrobial agents such as broad spectrum antibiotics (gentamicin sulphate, erythromycin or derivatized glycopeptides) which are slowly released into the tissue can be incorporated into the prosthesis to aid in combating clinical and sub-clinical infections in a surgical or trauma wound site.

To promote wound repair and/or tissue growth, one or several growth promoting factors can be introduced into the tubular prosthesis, e.g., fibroblast growth factor, platelet derived growth factor, macrophage derived growth factor, alveolar derived growth factor, monocyte derived growth factor, magainin, and so forth. To decrease abrasion, increase lubricity, etc., the prosthesis can be coated with copolymers of glycolide and lactide and polyethylene oxide, calcium salts such as calcium stearate, compounds of the Pluronic class, copolymers of caprolactone, caprolactone with PEO, polyHEMA, etc. Especially advantageous is a coating of hyaluronic acid with or without cross-linking.

Additionally, polypeptides such as Human Growth Factor (HGF) can also be coated upon or impregnated in the prosthesis to promote healing. The term "Human Growth Factor" or "HGF" embraces those materials, known in the literature, which are referred to as such and includes their biologically active, closely related derivatives. The HGFs can be derived from naturally occurring sources and are preferably produced by recombinant DNA techniques. Specifically, any of the HGFs which are mitogenically active and as such effective in stimulating, accelerating, potentiating or otherwise enhancing the wound healing process are useful herein, e.g., hEGF (urogastrone), TGF-beta, IGF, PDGD, FGF, etc. These and other useful HGFs and closely related HGF derivatives, methods by which they can be obtained and methods and compositions featuring the use of HGFs to enhance wound healing are variously disclosed, inter alia. in U.S. Pat. Nos. 3,883,497; 3,917,824; 3,948,875; 4,338,397; 4,418,691; 4,528,186, 4,621,052; 4,743,679 and 4,717,717; European Patent Applications 0 046 039; 0 128 733; 0 131 868; 0 136 490; 0 147 178; 0 150 572; 0 177 915 and 0 267 015; PCT International Applications WO 83/04030; WO 85/00369; WO 85/01284 and WO 86/02271 and UK Patent Applications GB 2 092 155 A; 2,162,851 A and GB 2 172 890 A, all of which are incorporated by reference herein. Of the known HGFs, hEGF, TGF-beta and IGF are preferred for use in the therapeutic composition of this invention.

The HGFs can be introduced with appropriate carrier such as carrier proteins disclosed, e.g., in "Carrier Protein-Based Delivery of Protein Pharmaceuticals", a paper of Biogrowth, Inc., Richmond, Calif., presented at a symposium held June 12-14, 1989 in Boston, Mass.

EXAMPLE 1

The following illustrates the manufacture of a ligament prosthesis as illustrated in FIG. 5.

A 420 denier composite yarn as illustrated in FIG. 1 was formed from a Hytrel 7246 yarn as the core component and a lactide (80 mole percent)-glycolide (20 mole percent) copolymer yarn providing the sheath component.

Six plies of the 420 denier composite yarn were wound onto 32 braider bobbins. The bobbins were loaded onto a 32 carrier braider to provide braided sheath 31. About one meter of the yarns from the 32 bobbins was pulled manually in parallel to provide a core 32 of 80,640 (420×6×32) overall denier. Application of braided sheath 31 also 420×6×32 or 80,640 overall denier resulted in ligament prosthesis 37 possessing an overall denier of 161,280. The stress (force in Newtons)-strain characteristics of prothesis 37 were measured and compared with the stress-strain characteristics of a human anterior cruciate ligament as reported in Noyes et al., *Journal of Bone and Joint Surgery*, Vol. 58-A, No. 8, p. 1074, et seq. (Dec. 1976). As shown in the plotted data of FIG. 6, the stress-strain characteristics of prosthesis 37 (continuous line) closely matched those of the natural tissue (broken line), an altogether remarkable achievement relative to known connective tissue prostheses.

EXAMPLE 2

The following illustrates manufacture of a tendon augmentation device 40 as illustrated in FIG. 7.

A 431 denier composite yarn as illustrated in FIG. 1 was formed from a Hytrel 7246 yarn to provide the core component 12, a lactide (80 mole percent)—glycolide (20 mole percent) copolymer yarn to provide the inner sheath component 14, and a lactide (10 mole percent)—glycolide (90 mole percent) copolymer yarn to provide the outer sheath component 16.

Six plies of the 431 denier composite yarn were wound onto 16 braider bobbins. The bobbins were loaded onto a 16 carrier braider to provide braided sections 42 and 43. About 70 mm of the yarn from the 16 braider bobbins was braided to form one of sections 42 and 43, and then the braiding was stopped. Then, about 35 mm. of the yarn from the 16 braider bobbins was pulled manually to form the unbraided center section 41, and then braiding was continued for another 70 mm of the yarn to form the other of sections 42 and 43. The resulting tendon augmentation device 40 had a total denier of 41,376 (431×6×16).

The tendon augmentation device 40 was implanted in a canine knee replacing the center third of the patellar tendon. Physical testing was carried out comparing two tendon augmentation devices 40 (TAD-1 and TAD-2) to the center third of the canine patellar tendon (½ P.T.) being replaced. More specifically, the stress (force in Newtons) —strain or load-deformation characteristics of devices 40 and the canine patellar tendon were measured and compared with one another.

As shown in the plotted data of FIG. 12, the responses of both tendon augmentation devices 40 (TAD 1 and TAD 2) were very similar to the one third canine patellar tendon. Moreover, tendon augmentation devices 40 (TAD 1 and TAD 2) were generally stronger than the replaced canine patellar tendon which failed when too great a load was applied thereto.

EXAMPLE 3

A composite yarn as illustrated in FIGS. 3 and 4 was fabricated using Hytrel 7246 fibers as the core component 33 and bioabsorbable sheath component fibers 35 of two different chemical compositions: first bioabsorbable fibers 35′ fabricated from an 80 mole percent lactide/20 mole percent glycolide copolymer, and second bioabsorbable fibers 35″ fabricated from a 10 mole percent lactide/90 mole percent glycolide copolymer. The first bioabsorbable fibers 35′ were formed into yarn bundles, each yarn bundle comprising 12 filaments and having a total denier of 24. The second bioabsorbable fibers 35″ were also formed into yarn bundles, each yarn bundle comprising 17 filaments and having a total denier of 27.

The composite yarn was formed using three Hytrel yarn bundles, each Hytrel yarn bundle comprising 70 filaments, to form a core component 33 of approximately 270 denier. The braided sheath component 34 was formed around the Hytrel core component 33 using an 8 carrier braider, 4 carriers each of the first and second bioabsorbable yarn bundles. The composite yarn thus formed exhibited a tensile strength of 3.19 grams/denier, and is suitable for use in fabricating a connective tissue prosthesis of the present invention.

What is claimed is:

1. A connective tissue prosthesis comprising:

a) a core made up of a first biocompatible composite yarn extending in a lengthwise direction; and

b) a sheath surrounding the core, said sheath being fabricated from a second biocompatible yarn;

the first composite yarn in said core (a) comprising a non-bioabsorbable core yarn component surrounded by an at least semi-bioabsorbable sheath yarn component.

2. The connective tissue prosthesis of claim 1, wherein the second biocompatible yarn in said sheath (b) comprises a non-bioabsorbable core yarn component surrounded by an at least semi-bioabsorbable sheath yarn component.

3. The connective tissue prosthesis of claim 2 wherein the sheath yarn component is bioabsorbable.

4. The connective tissue prosthesis of claim 1 exhibiting stress-strain characteristics approximately those of the natural connective tissue replaced or augmented by the prosthesis.

5. The connective tissue prosthesis of claim 1 wherein said connective tissue prosthesis is a ligament or tendon prosthesis.

6. The connective tissue prosthesis of claim 1 wherein said connective tissue prosthesis is a human anterior cruciate ligament prosthesis.

7. The connective tissue prosthesis of claim 1 in which the core component comprises at least one filament.

8. The connective tissue prosthesis of claim 7 in which the core (a) of the prosthesis comprises multiple composite yarns.

9. The connective tissue prosthesis of claim 7 wherein the core component comprises multiple filaments.

10. The connective tissue prosthesis of claim 1 in which the sheath component comprises at least one filament.

11. The connective tissue prosthesis of claim 10 wherein the sheath yarn component comprises multiple filaments.

12. The connective tissue prosthesis of claim 1 in which the core component is manufactured from at least one polymeric material selected from the group consisting of polyethylene homopolymers, polypropylene homopolymers, ethylene-propylene copolymers, ethylene propylene terpolymers, fluorinated hydrocarbons, fluorosilicones, isobutylenes, isoprenes, polyacrylates, polybutadienes, polyurethanes, and polyether-polyester copolymers.

13. The connective tissue prosthesis of claim 1 in which the core component possesses an elongation at break of at least about 30 percent.

14. The connective tissue prosthesis of claim 1 in which the sheath component is an absorbable, relatively inelastic polymeric material derived at least in part from a monomer selected from the group consisting of glycolic acid, glycolide, lactic acid, lactide, p-dioxanone, trimethylene carbonate, e-caprolactone and hydroxycaproic acid.

15. The connective tissue prosthesis of claim 1 in which the sheath component is a lactide-glycolide copolymer.

16. The connective tissue prosthesis of claim 12 in which the sheath component is a lactide-glycolide copolymer containing from about 70 to about 90 mole percent lactide units.

17. The connective tissue prosthesis of claim 16 in which the sheath component is a lactide-glycolide copolymer containing from about 75 to about 85 mole percent lactide units.

18. The connective tissue prosthesis of claim 1 wherein the sheath (b) covering the core (a) is at least partially woven.

19. The connective tissue prosthesis of claim 18 wherein the sheath (b) is entirely woven.

20. The connective tissue prosthesis of claim 1 further comprising at least one bioactive substance.

21. The connective tissue prosthesis of claim 1, wherein said sheath component is helically wound about said core component.

22. The connective tissue prosthesis of claim 21, additionally comprising

a second sheath component helically wound about said sheath component in a different direction.

23. The connective tissue prosthesis of claim 22, in which said second sheath component is a lactide-glycolide copolymer.

24. The connective tissue prosthesis of claim 22, wherein said first and second sheath components have different ratios of absorption.

25. The connective tissue prosthesis of claim 1, wherein said sheath component is braided around said core component.

26. The connective tissue prosthesis of claim 25, wherein said sheath component comprises a plurality of bioabsorbable fibers, said fibers comprising at least two different chemical compositions.

27. The connective tissue prosthesis of claim 1, wherein said core (a) and sheath (b) together are branched at discrete locations to form gaps between branches of said prosthesis.

28. The connective tissue prosthesis of claim 27, wherein a yarn is wrapped about said sheath (b) at discrete locations to at least temporarily retain said sheath (b) about said core (a).

29. The connective tissue prosthesis of claim 28, wherein said wrapping yarn comprises a biocompatible, non-bioabsorbable core yarn component surrounded by a at least semi-bioabsorbable sheath yarn component.

30. The connective tissue prosthesis of claim 29 wherein said sheath component of said wrapping yarn is bioabsorbable.

31. The connective tissue prosthesis of claim 1 wherein said sheath yarn component is bioabsorbable.

32. The connective tissue prosthesis of claim 1 wherein the sheath (b) covering the core (a) is at least partially braided.

33. The connective tissue prosthesis of claim 32 wherein the sheath (b) is entirely braided.

34. The connective tissue prosthesis of claim 1 wherein the sheath (b) covering the core (a) is at least partially knitted.

35. The connective tissue prosthesis of claim 34 wherein the sheath (b) is entirely knitted.

36. A connective tissue prosthesis comprising:

a tubular component fabricated from composite yarn, said yarn comprising a biocompatible, core yarn component surrounded by a biocompatible, at least semi-bioabsorbable sheath yarn component.

37. The connective tissue prosthesis of claim 36, comprising a center section where said yarn is unbraided and bordered by sections where said yarn is braided.

38. The connective tissue prosthesis of claim 37, additionally comprising

a helical wrap about said unbraided center section.

39. The connective tissue prosthesis of claim 38, wherein said helical wrap is fabricated from composite yarn comprising a biocompatible, non-bioabsorbable core yarn component surrounded by a biocompatible, at least semi-absorbable sheath yarn component.

40. The connective tissue prosthesis of claim 39, wherein said sheath component is bioabsorbable.

41. The connective tissue prosthesis of claim 36, additionally comprising

a threading member attached to an end thereof, said threading member comprising a composite yarn which comprises a biocompatible, non-bioabsorbable core yarn component surrounded by a biocompatible, at least semi-bioabsorbable sheath yarn component.

42. The connective tissue prosthesis of claim 41 wherein said sheath component is bioabsorbable.

43. The connective tissue prosthesis of claim 36 wherein said sheath component is bioabsorbable.

44. Methed for manufacturing a connective tissue prosthesis, comprising

forming said connective tissue prosthesis from a first biocompatible composite yarn comprisung a non-bioabsorbable core yarn component surrounded by an at least semibioabsorbable sheath yarn component.

45. The method of claim 44, wherein said connective tissue prosthesis comprises a core and a sheath, said core being at least partially surrounded by said sheath.

46. The method of claim 45, wherein said biocompatible composite yarn forms said core.

47. The method of claim 44, wherein said biocompatible composite yarn forms said sheath.

48. The method of claim 44, wherein the sheath is woven about the core.

49. The method of claim 48, wherein

the sheath is braided from braider bobbins loaded onto a carrier braider, and

the core is pulled through the thus-braided sheath.

50. The method of claim 48 wherein the sheath is braided about the core.

51. The method of claim 44 wherein said sheath component is bioabsorbable.

52. The method of claim 44 wherein the sheath is knitted about the core.

53. Method for manufacturing a tubular connective tissue prosthesis, comprising

forming a tubular component from composite yarn comprising a biocompatible, non-bioabsorbable core yarn component surrounded by a biocompatible, at least semi-absorbable sheath yarn component.

54. The method of claim 53 wherein the tubular component is formed by weaving.

55. The method of claim 53 wherein the tubular component is formed by braiding.

56. The method of claim 55, wherein the tubular component is braided from braider bobbins loaded onto a carrier braider.

57. The method of claim 53 wherein the tubular component is formed by knitting.

58. The method of claim 53 wherein the sheath component is bioabsorbable.

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